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CONGENITAL BILIARY ATRESIA

REPORT OF THREE CASES; TWO OCCURRING IN ONE FAMILY

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SCATTERED throughout the literature are numerous reports of congenital atresia of the extrahepatic biliary system, and it is the purpose of this paper to summarize and bring up to date some of the more important practical concepts of this subject. Although the occurrence of this congenital lesion has been known for many years, it having been first described by Aristotle, it was not until John Thomson[1, 2] collected fifty cases in 1891 that a real survey was made of the subject. Probably the first case of surgical intervention was that attempted by Giese and Witzel[3] in 1895, while Putnam and Elliot[4] operated on a 4-month-old female infant in 1898 who died on the third postoperative day. In 1916, Holmes[5] summarized 112 cases and concluded that approximately 16 per cent were theoretically operable, based on pathological findings. Stolkind[6] collected 245 cases in 1939 and at least eighteen additional cases have been individually cited since that time. In a review of 21,000 admissions, Donovan[7] found sixteen cases of congenital atresia of the biliary system. There does not seem to be any significant sex predominance as Amberg[8] pointed out in a series of eighteen cases in which there were ten girls and eight boys.

A report of the familial occurrence of this anomaly was first made by Gould[9] in 1855 in which there were two cases in one family, while in 1866 Binz[10] also demonstrated two cases of biliary atresia dying within forty-eight hours of birth, although the father showed evidence of syphilis. Sweet[11] observed three patients, two of whom were operated upon unsuccessfully. These cases were essentially the same, having both intra- and extrahepatic biliary malformation together with cardiac anomalies in two cases. There was no evidence of maternal toxemia, infection, or trauma in Sweet's cases. Hopkins[12] also reported three cases in which the mother had a mild toxemia in all of her pregnancies, and whose sister had chronic jaundice. Of six pregnancies, twin girls were born at eight months with jaundice which cleared up in a few weeks. Two years later a third female was born at eight months with icterus and died on the second day showing a nonpatent ampulla of Vater. The fourth sibling had no icterus, but had an enlarged liver and died on the seventh day because of absence of part of the common bile duct. The fifth and seventh babies were aborted at seven months, but were not autopsied, while the sixth child was full term and icteric, dying at three days with evi-

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dence of occlusion of the lower end of the common duct. It is evident therefore that more than three of the offspring may have been affected.

Numerous other instances have been cited as cases of familial biliary malformation, but most of these have only autopsy findings from one sibling and presumptive evidence of a similar anomaly through clinical observation of from one to five other patients in each family. Those with such unproved cases include Gordon,[13] West,[14] Thomas,[15] and Glaister.[16] Probably the largest familial incidence in these presumptive cases was reported by Dunbar[17] where one autopsied patient showed hepatomegaly and completely occluded bile ducts at 7 months of age. Of ten other siblings, five were born jaundiced and died within a few weeks of life without post-mortem examination, thereby suggesting a possible total of six cases in one family. Arkwright,[18] Bloomfield,[19] and Pearson[20] also reported cases of familial icterus at birth claiming that they were from biliary obstruction, but because of the lack of post-mortem examination and an unsuggestive history these cannot be considered. To summarize then, there have been four proved instances of a familial tendency toward congenital biliary malformations, and four suggestive cases, not counting our own cases.

EMBRYOLOGY

Although many theories have been advanced to explain this anomaly, probably the most sound proposes that a defect in the germ plasm probably arrests the normal embryological development. As has been described by Ylppo[21] and others, the epithelial lining of the liver and of the biliary system is derived from the entodermal tube. During the third week the anlage of the liver, which is a mass of anastomosing trabeculae, joins the elongated diverticulum from the entodermal tube by a solid cell stem, which will be the hepatic duct. The caudal cells of the diverticulum proliferate thereby creating the extrahepatic biliary system. Rapid cellular hyperplasia however occludes the lumen until the fourth month when clefts appear between the cells and they join together to re-establish the lumen just before the fifth month which is one month previous to the production of bile. The order of succession of the appearance of the lumina is the common bile duct, hepatic duct, cystic duct, and the gall bladder. As Chesterman[22] points out, irregular cleft formation, atypical fusion, or lack of canalization can cause partial or complete atresia and accessory ducts.

As is evident from the complex developmental anatomy of the biliary system, innumerable anomalies are possible, making classification difficult. Ladd and Gross[32] in reviewing forty-five cases found only the hepatic duct patent in three cases, the hepatic and part of the common duct patent in six cases, atresia of the hepatic duct with the remainder of the biliary system normal in five cases, and complete atresia or absence of the extrahepatic ducts in thirty-one cases. Other possibilities which they present include stenosis of the common duct with or without a biliary plug, a cystlike gall bladder which is not connected with the common ducts in which the common duct or hepatic duct may or may not be present, and a situation in which the gall bladder may be connected with the duodenum with com-

plete absence of the biliary tract. Gordon[13] lists an additional, somewhat controversial type in which there is obliteration of the intrahepatic ducts with a patulous gall bladder and an entirely normal extrahepatic ductal system.

Another classification of anomalous gall bladders is that of Stolkind.[6] Primarily it may be absent, rudimentary, or be merely a fibrous cord. It may be double with either two completely separate gall bladders or be bilobed. As to location, it may be partially or entirely embedded in the liver, or may hang freely suspended from the liver. Of course, if there is complete or partial transposition of the viscera, the gall bladder may be left-sided.

Associated congenital anomalies also occur as reported by Amberg and Zuschlag,[24] where they found four of their eighteen cases had congenital cardiac lesions together with other malformations such as situs inversus, multilobulation of the spleen, accessory spleens, a hydrocele in a patient with micrognathia, and one patient with cysts of the cystic duct and an ovary. Stolkind[6] also reported several cases with congenital hearts. In the three cases in one family cited by Sweet,[11] two also had associated cardiac abnormalities.

Various hypotheses have been postulated to explain these anomalies. Howard and Wolbach[25] feel that there is some truth in all the theories in that some cases may be due to an anomaly of development, others to a simple inflammation of the ducts and still others to a primary congenital cirrhosis, but that no one theory could suffice for all cases. It is most generally accepted that probably this is a result of a germ plasm defect.

CLINICAL AND LABORATORY FINDINGS

Jaundice.—The presence of jaundice in a newborn infant should make one think of the possibility of biliary atresia and its persistence should make one carry out suitable procedures to rule it out. The results of delay are illustrated in the first case where the patient was not investigated until 8 months of age, having been neglected at home. Estimates of the incidence of jaundice at birth vary from 30 to 80 per cent, but despite this wide spread it is known that the cord serum bilirubin is elevated, ranging from 1 to 2 mg. per 100 c.c. normally. Jaundice, however, does not become as evident in newborn infants because of the erythema of the skin for the same serum bilirubin level as in adults where over 2.5 mg. per 100 c.c. demonstrates icterus. Various estimates have been made as to what level is needed, ranging from 1.25 mg. per 100 c.c. to 12 mg. per 100 c.c., while others appeared normal at 12 mg. with the average patient, showing clinical icterus was about 5 mg.[26, 27]

Actually the jaundice caused by congenital biliary atresia is rarely demonstrable at birth, occurring most frequently between the fifth and fourteenth days, although occurrences as late as three weeks have been reported. Probably jaundice at birth is not physiological; however, as will be pointed out later, icterus neonatorum precox does occur.[28] It is thought by most that the jaundice persists and becomes constantly more severe, but Chesterman[22] felt that it varied from day to day and Amberg[24] postulated that it recedes in some cases probably because of a decrease in the formation of bile, due to liver damage. Generally speaking, the icterus does progress steadily

and in Ladd and Gross's[32] series it varied between 50 and 325 with an average of 125. Rapoport[33] pointed out that as the jaundice increases it changes from a dark yellow to an olive green due to presence of the oxidation product of bilirubin, namely, biliverdin. Because of this he advocated following the progress of these cases via the icteric index rather than the serum bilirubin since biliverdin does not produce any color in the van den Bergh test, which in these cases produced an immediate direct reaction.

The Abdomen.—The abdomen usually does not demonstrate any positive physical findings at birth although the liver may be slightly enlarged. As the child becomes older, however, the liver gradually enlarges and frequently descends to the level of the umbilicus where one can feel a firm smooth edge. The spleen which is of normal size at birth also tends to enlarge and becomes readily palpable as the obstruction continues. The abdomen not only appears distended from these enlarging viscerae, but because of portal obstruction and cirrhosis, ascites develops, causing in some cases marked enlargement, with prominent superficial veins.

The Stools.—It has been said by some that the stools are always white or clay colored, having a pasty or putty-like consistency, but Gellis and Sisson[28] point out that the meconium may have a normal green color as it is formed at the fourth month of gestation, and unless blockage of the biliary tract has occurred before this, it will be normal in color. Following this normal stool, the intestinal contents become alcoholic as described although in cases where the jaundice is of great intensity the outside of the stools may be bile tinged due to secretion of bile through the intestinal wall and the adherence of desquamated cells from the intestinal mucosa. This usually occurs in the older more advanced cases.

The Urine.—The urine, of course, reflects the findings seen in the icteric index, but it becomes dark shortly before the appearance of clinical jaundice. There is a persistently high bilirubin level, but occasionally urobilinogen can be detected early in the disease, although it disappears rapidly. There are no other urinary findings to suggest any evidence of kidney dysfunction such as one might see in the so-called hepatorenal syndrome.

The Blood.—The red cell count is usually unremarkable, there being frequently only a slight anemia varying from 3.5 to 4 million cells. In the red series no immature cells are ordinarily seen and the fragility is not increased. No abnormalities in the white cells are evident unless infection supervenes, such as in the terminal episode. The platelet count is usually normal, but because of poor vitamin K absorption, hypoprothrombinemia frequently results. In two cases Ladd and Gross[34] noted one normal prothrombin time, but a diminution to 60 per cent of normal in another. Gonce[35] reported an alteration of 55 and 15 per cent. The clotting time has not been noted above six to seven minutes while the bleeding time is essentially normal. Vitamin K deficiency, however, is less frequent than might be expected, and it is not until after six months of obstruction that the liver cannot form prothrombin and bleeding results. This is not infrequently the terminal result and hemorrhage from the nose, gastrointestinal tract, umbilicus, mucous membranes, and the skin occur.

Ylppo[29] reported a case of cerebral cortical hemorrhage as did Amberg and Zuschlag[24] while Ladd and Gross had a terminal case with intraperitoneal bleeding.

Metabolism.—The general nutrition in this condition is fairly good with no particular anorexia present, and constipation is more commonly observed than diarrhea. Physical development is somewhat retarded, however, and there is an eventual loss of subcutaneous fat.

Koplik and Crohn[36] have shown that nitrogen metabolism was unaltered and this was corroborated by Neiman[37] who observed nitrogen absorption of 80 to 93 per cent. With the absence of bile salts, splitting and saponification of neutral fats is diminished, activation of pancreatic lipase is retarded, and absorption of fat is decreased. Gonce[35] demonstrated the degree to which this was present by observing that 80 per cent of the dried weight of the stools was fat as compared with a normal of 20 to 35 per cent. An analysis of this fat showed 8 per cent neutral fat (normal 10 per cent), 42 per cent free fatty acids (normal 20 per cent), and 50 per cent soap (normal 70 per cent).

Limitation of fatty absorption naturally results in deficiencies of the fat-soluble vitamins. Rapoport[33] found a deficency of vitamin A in five out of six infants living six months or more, and Thoenes and Gurson[38] showed that xerophthalmia would not respond to oral vitamin A, but would to parenteral. The presence of bile has been shown experimentally by Heyman[39] to be necessary for the absorption of vitamin D and therefore the presence of rickets and osteoporosis is not rare. Gonce[35] and Amberg[24] each had two cases of osteoporosis, and as pointed out by Davidson, Merritt, and Weech,[30] pathological fractures may occur. The use of oral vitamin D, in dosages as large as 23,300 units, was shown by Park and Eliot[40] to cause only a slight deposition of calcium salts, while daily administration of molar citric acid created a marked response. Ultraviolet radiation has also helped in some of these cases.

Although absorption of vitamin K is retarded, a deficiency state is less frequent than might be expected. Prothrombin time determinations have varied from normal to 15 per cent in various cases. After six months, however, the liver is sufficiently damaged to cause a diminished formation of prothrombin and bleeding may result.

Carbohydrate absorption is normal but with the progression of cirrhosis, liver glycogen storage and liberation is impaired markedly and a hypoglycemic state is established, particularly in older infants.

DIFFERENTIAL DIAGNOSIS

Inspissated bile plugs can cause a picture similar to congenital atresia and may occur concomitantly with icterus neonatorum possibly because of excessive hemolysis causing viscid bile, or a foreign substance in the bile causing coagulation.[42] The clinical picture may exactly simulate that of atresia, although intermittent jaundice frequently occurs. Snelling[41] recommends administration of 20 per cent magnesium sulfate and bile salts by duodenal tube with feeding in an attempt to aid passage of the biliary plug.

Icterus neonatorum or physiological jaundice generally occurs from the second to the fourth day and may last from three to twenty-one days. There

is no hepatosplenomegaly or anemia present and the stools and urine are normal in appearance. The presence of jaundice during the first twenty-four hours is considered to be pathological by Halbrecht[31] and is designated as icterus neonatorum precox, the mechanism of its production being the passage of anti-A and anti-B isohemoagglutinins from the mother to the infant, causing hemolysis of erythrocytes with the production of an excessive amount of bilirubin and resultant jaundice.

Erythroblastosis fetalis should, of course, be suspected prenatally because of the potential Rh incompatibility of the mother with an Rh-positive father. With a history of previous deliveries or of transfusions the possibility of this condition becomes increasingly more evident. Examination of the cord blood shows a reduced serum protein and prothrombin concentration together with a macrocytic anemia composed of erythroblasts and normoblasts in an elevated number. The Coombs test is positive. The occurrence of erythroblastosis and biliary atresia has been reported and must be considered. Icterus may be mild at first but progresses rapidly in the severe cases because of extensive hemolysis. The presence of yellow vernix caseosa and placental hypertrophy is always suggestive of this condition. Splenomegaly, together with liver enlargement, tends to differentiate this situation from biliary atresia also. Early realization of the existing problem is, of course, of great import in the disease.

Sepsis may well present a picture of hepatosplenomegaly together with an increased number of erythroblasts; however, the occurrence of jaundice follows the development of the infection by a few days, and the presence of toxicity, leukocytosis, positive blood cultures, elevation of temperature plus a focus of infection indicate this condition. The fact that febrile reaction to sepsis frequently is absent in infants is worthy of note. The urine and stools, of course, are normal.

Congenital syphilis seldom leads to confusion in its differentiation from biliary obstruction. Presence of hepatosplenomegaly, anemia, many erythroblasts in the blood, various stigmas, a positive serology, typical long bone changes by x-ray and a history of maternal infection make this condition evident although it may be confused with erythroblastosis in rare cases.

For the sake of completeness, hemorrhagic disease of the newborn and congenital acholuric jaundice should also be mentioned.

The following three cases were observed in the New Rochelle Hospital between 1943 and 1950.

CASE REPORTS

CASE 1 (121731).—J. H., an 8-month-old white male, was admitted Jan. 17, 1944, with a history of jaundice since birth which had become progressively more marked. The patient's condition had been unrecognized at home, however, and suitable studies were not done until the time when he was brought to the hospital. The stools had been constantly clay colored and the urine dark. Physical examination revealed a marasmic icteric infant weighing 9 pounds 14 ounces, with a temperature of 97° F., and appearing acutely ill. The sclerae were markedly jaundiced as was the skin. There were some enlarged anterior cervical nodes, and a thick mucous discharge was present in the nose. The cardiovascular system was within normal limits, but the lung fields were filled with numerous coarse râles. The abdomen was

markedly distended with prominent superficial veins and evidence of ascites. The liver extended 6 cm. below the right costal margin and was firm while the spleen was similarly enlarged. A right indirect inguinal hernia was also present. Deep tendon reflexes were hypoactive.

Laboratory findings revealed a red cell count of 3,200,000 with a hemoglobin of 64 per cent and a color index of 1.0. The white cell count was 12,600 with 33 per cent neutrophils, 59 per cent lymphocytes, and 8 per cent mononuclear cells. Urinalysis revealed one plus albumin and gave a positive test for bile. The icteric index was 146, while the serum bilirubin was 25 mg. per cent. A red cell fragility test was done in which hemolysis began at 0.38 per cent and was completed at 0.34 per cent. The cephalin flocculation test was four plus.

X-rays of the abdomen demonstrated considerable enlargement of the right lobe of the liver with generalized abdominal enlargement, while the chest was reported as having only a slight increase in hilar shadows.

The infant had a rapid downhill course and died on the eighth hospital day.

Post-mortem examination revealed the liver to be moderately enlarged and the bile duct radicles were not recognizable grossly. The gall bladder was small and contained pale opal-colored mucus. The cystic duct was short and recognizable only as a white fibrous cord about 1 mm. in diameter. The common bile duct could not be located.

Microscopically the liver showed a coarse pattern of cirrhosis with broad strands of scar about the portal canals and surrounding irregularly shaped islets of liver cells. Numerous small bile duct radicles were scattered through the fibrous tissue, but they were compressed and contained no bile.

CASE 2 (156291).—R. H., a 5½-month-old white male, was admitted to the New Rochelle Hospital Oct. 23, 1947, with a chief complaint of jaundice which had been noted at birth, and although the intensity had varied, the icterus had become progressively more severe. The stools had been a grayish white and the urine appeared excessively dark. The infant's appetite had been fairly good, but within a month of admission, weight gain had diminished. There had been no vomiting, diarrhea, or constipation.

Past history revealed a full-term uneventful delivery following an uncomplicated pregnancy. Pertinent data regarding the family pertained only to the occurrence of biliary atresia in a sibling.

Physical examination showed the patient to be fairly well nourished and slightly jaundiced. The respiratory and cardiovascular systems were within normal limits. The abdomen appeared distended with the liver palpable three fingerbreadths below the right costal margin, and the spleen just palpable. Weight was 12 pounds 8 ounces, temperature 98.4° F.

Initial laboratory studies revealed 4,300,000 erythrocytes per cubic millimeter with 89 per cent hemoglobin. The white cell count was 13,000 with 85 per cent lymphocytes, 13 per cent neutrophils, 1 one cent eosinophils, 1 per cent basophils, and platelets 266,000. The urine was within normal limits. There was a trace of urobilin. Wassermann test was negative. The bleeding time was 2 minutes 15 seconds, while the coagulation time was 3 minutes 30 seconds. Icteric index was 18 with an indirect van den Bergh of 4.8 mg. per cent and a delayed positive direct van den Bergh. Thymol turbidity was 33 units (normal up to 6), but the Hanger cephalin flocculation test was negative. The tests for prothrombin activity showed 16.6 seconds undiluted and 43 seconds diluted 12.5 per cent. Alkaline phosphatase was 15.5 units while examination of the stools for bile pigments was negative. The red cell fragility test was within normal limits. Roentgenologically the gall bladder could not be demonstrated by the use of oral Priodax. These studies were interpreted as obstructive jaundice with mild liver damage.

The infant's course in the hospital was uneventful except for a short period of projectile vomiting and a bulging anterior fontanel. Spinal fluid examination was unremarkable and the patient was able to retain food shortly afterward. The jaundice progressed rapidly, and on Nov. 19, 1947, an exploratory laparotomy was performed.

The common bile duct was found to be present and although somewhat small and thickened, appeared natural down to within 8 mm. of the duodenum where it faded away into a fibrous cord in which a lumen could not be successfully demonstrated. A cholecystoduodenostomy in the midportion of the gall bladder was performed.

Postoperative Course.—The child survived the operation well although he had a temperature of 103° F. for the first postoperative day. He was given 5 per cent glucose and water after the first twenty-four hours which was changed to a half strength skimmed milk formula and gradually increased. Although the patient looked well, the jaundice continued to progress, the icteric index increasing from 67 two days postoperatively to 100 six days later. This phenomenon also occurred in the third case although a rubber cannula was not used to bridge the anastomosis. A yellow stool was passed on the third postoperative day, but it was not until the sixteenth postoperative day that the stools were reported positive for bile pigments. The rubber catheter was never recovered in the stools. The patient continued to improve, and on Dec. 24, 1947, he was discharged, weighing 13 pounds 4 ounces and eating well.

The last report obtained on this child at the age of 4 years, 9 months is that he weighs 44 pounds and measures 44 inches. He tolerates his diet without digestive disturbance and eats three meals a day without restriction of food. He has normal bowel movements and the character of the stools is within normal limits. The mother states that he enjoys excellent health and seems to be developing normally.

CASE 3 (183670).—G. R., a newborn, full-term baby boy, apparently normal, weighing 5 pounds 9 ounces at the time of birth, April 23, 1950. Within the first twenty-four hours he took water, was fed at the breast, and was given a formula. The skin was of a normal color, and the stool was yellowish tinged.

On April 25, 1950, the baby had edema of the ankles, was observed to be pallid and there was hematemesis and rectal bleeding. The urine was dark in color. To replace the loss of blood a transfusion of 68 c.c. of blood was given. On April 28 the eyelids became swollen, the skin was distinctly jaundiced, and the stools became gray colored. On the fifth day of life the red blood cell count was 6,200,000 with 23.4 grams of hemoglobin. The white blood cell count was 7,100 with 19 segmented and 23 nonsegmented forms. There were 9 eosinophils and 35 lymphocytes. The urine was a dark yellow color, showed albumin one plus, and was positive for bile. The patient continued to take feedings well and by the end of the first week the jaundice had cleared somewhat. On the eighth day the white blood cells were 11,100 with 27 segmented and 10 nonsegmented. The bleeding time was 1 minute and the coagulation time 3.5 minutes. The feedings were supplemented by hypodermoclysis each day. The skin remained elastic and was jaundiced, as were the sclerae. On the twenty-sixth day after birth the baby weighed 6 pounds, the liver was about 3 cm. below the costal margin, and the jaundice was clearing gradually. Tests to determine the degree of jaundice were not done on account of the difficulty in obtaining blood. The patient was discharged from the hospital with a diagnosis of partial atresia of the bile ducts.

For one week he seemed to do fairly well, but the color of the skin did not return to normal. After another week a gradual deepening of the jaundice, a loss of weight, and return of clay-colored stools occurred. The baby was readmitted to the hospital on June 6, and because of the marked change in

his condition suggesting an increase in the obstruction to the outflow of bile, surgical exploration was decided upon. He was prepared by blood transfusion, vitamin K, hypodermoclysis, and penicillin.

At operation on June 9, 1950, the liver was found to be enlarged and of a dark green color. The hepatic ducts, the cystic duct, and the gall bladder were present. The common duct was markedly narrowed. There was inflammatory reaction involving the common duct, and the tissues about it. The lumen seemed to be patent, but so small that a 22 gauge needle could not be inserted. It was contracted and cordlike from the cystic duct to the duodenum. The remaining portion of the visible biliary duct system did not appear to be inflammatory. A cholecystoduodenostomy was done.

The immediate postoperative course was uneventful except that on the fourth day the jaundice which had cleared slightly became much deeper. This lasted for three days and then began to subside. The patient ate well directly after operation and by the fourth day was gaining weight. The stools became bile stained on the fifth day.

He was sent home on the seventeenth day with the wound well healed and the general condition greatly improved. By the end of the fourth week after operation the skin had returned to normal color. Eighteen months after the operation the baby measured 32 inches in length and weighed 25 pounds 9 ounces. There were no digestive disturbances.

FOLLOW-UP STUDIES

Because there was evidence of liver damage and alteration of body metabolism in R. H. (Case 2), this child was followed with serial laboratory examinations following discharge in order to establish the rapidity and completeness of return to normal function.

As has been noted by Ladd and Gross,[34] the function of the alimentary tract appeared to be physiological, there being no anorexia, alteration in the character of the stools, or intolerance to fatty substances. The possibility of ascending cholangitis must be considered but abdominal pain, fever, or jaundice was not observed, and only one such case has been reported, this being mild in character.

It has been suggested by some authors that biliary obstruction may well cause irreversible liver damage thereby contraindicating operative intervention. This has not been observed clinically, however, apparently because of the marked powers of regeneration of the liver. Generally speaking, however, surgery should be attempted before the fourth month because of secondary systemic complications. In Case 2 the thymol turbidity test which was 36 units at operation dropped to a normal of 4 units within a period of six weeks. The significance of the negative Hanger cephalin flocculation test, which was negative preoperatively and one plus six weeks later, is doubtful. Since the total proteins, albumin-globulin ratio, and bleeding and coagulation times were all normal, no changes were anticipated. The icteric index was 16 six weeks postoperatively, although the serum bilirubin was still moderately elevated at 3.1 mg. per cent. The latter, however, when tested one month later, was a normal 0.5 mg. per cent.

The alkaline phosphatase level was followed pre- and postoperatively, varied inconsistently, but was normal ten weeks after surgery. As was shown by Carr and Foote[43] experimentally in dogs, the amount of alkaline phosphatase may rise temporarily following the relief of biliary obstruc-

tion and may still be elevated as long as two weeks after the serum bilirubin is normal.

The possible occurrence of the hepatorenal syndrome has been postulated by some, but has not been observed clinically. Wilensky[44] suggested the presence of a nephrotoxic agent liberated by the liver, particularly in chronic gall bladder disease, creating not only kidney damage, but changes in all organs such as the heart.

Abnormalities in the function of the gastrointestinal tract have been investigated using barium studies, and distortion of the gastric antrum, pyloris, or duodenum has been observed, but clinically no anorexia, postprandial distress, nausea, or vomiting was noted in any of the cases[34] and this was true also in this case.

SUMMARY

The occurrence of familial biliary anomalies is reviewed. Three cases are presented, two of which were successfully operated upon. Follow-up studies of liver function are presented in the second case to demonstrate the reversibility of hepatic damage in this disease.

We wish to thank Dr. Fairfax Hall and Dr. David Mass for permission to use the clinical material in the second and third cases, respectively.

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ACUTE GLOMERULONEPHRITIS IN CHILDHOOD

A Study of the Late Prognosis of Twenty-seven Cases

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INTRODUCTION

ONE of the most controversial questions with regard to glomerulonephritis is whether the acute and chronic forms of bilateral nonpurulent kidney disease are two diseases with different etiology, or whether acute nephritis is the initial stage of a continuous pathological process, the result of which is manifested either by healing or by the terminal stage of chronic nephritis.

In general, physicians who treat adults take the latter view, while physicians experienced with the treatment of children favor the former. This is reflected in the literature by statistics which appear to indicate that a large percentage of adults with acute nephritis progress to the chronic state, while the figures for children are much more encouraging. Bradley and associates[1] state that, "Although accurate figures are difficult to obtain, it is generally stated that about 95 per cent of the acute glomerulonephritis in childhood heals whereas only about 60 per cent of the acute glomerulonephritis in adults heals."

Several factors peculiar to the study of the disease may explain this apparent discrepancy, among these the following: (a) the etiology of Bright's disease remains a mystery, which has led to (b) a basis of classification which depends largely upon clinical observation, undoubtedly contributing to significant distortion of statistical studies; (c) misinterpretation by the physician of the patient's history may lead to error in classification, in cases which are seen by him initially in the chronic state; (d) it cannot be stated with certainty, particularly with regard to older children or adults, that an acute attack is not an exacerbation of an already existing disease process.

In recent years, interest in glomerulonephritis has increased, because of the hope for prevention or cure by some of the new therapeutic agents. No more discouraging ailment exists for the pediatrician or internist alike to treat than chronic nephritis, and none which offers slimmer hope for the patient. Cabot[2] said, in 1917, "With respect to the prognosis of nephritis . . . the first thing to be said, I think, is that in acute nephritis one should never give up a case until the patient is dead. . . . On the other hand, I suppose it is fair to say that no case of chronic nephritis ever recovered, and . . . no case of chronic nephritis ever will recover."

It is therefore imperative that, until the cause and prevention of Bright's disease are discovered, every means be made available for accurate prognosis.

Aldrich[3] was convinced by his clinical observations that the overwhelming majority of children who are

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stricken with acute nephritis recover completely. The purpose of this paper is to report a follow-up study of a series of patients observed by him and his associates between 1918 and 1931, and to suggest that this report and similar long-term studies may add assurance to the physician's prognosis and comfort to the victims of this malady.

REVIEW OF THE LITERATURE

Results of studies of the prognosis of acute glomerulonephritis which have

TABLE I. SUMMARY OF STUDIES, 1919 TO 1950, TO DETERMINE THE LATE PROGNOSIS OF ACUTE GLOMERULONEPHRITIS IN CHILDHOOD

AUTHOR	YEAR	NUMBER OF CASES	TIME OF OBSERVATION	RESULTS
Hill[6]	1919	49	----------	84% recovered.
James[7]	1921	67	Up to 16 yr.	86% recovered, 9 developed chronic nephritis.
Osman[8]	1925	56	1½ to 22 yr.	64% recovered.
Clausen[9]	1926	102	----------	71% recovered, 9 cases terminated with chronic nephritis.
Paterson, Wyllie[10]	1926	49	3 to 5 yr.	Classification is not clear. 5 of 22 cases of "acute parenchymatous type" recovered completely. 12 of 27 "acute hemorrhagic type" recovered completely.
Blackfan[11]	1926	24	----------	21 recovered, 3 died of uremia.
Boyd[12]	1927	50	2 to 5 yr.	72% recovered. 12% died, 16% chronic.
Lyttle, Rosenberg[13]	1929	38	1 to 7 yr.	89% recovered, 4 cases became chronic.
Guild[14]	1931	34	1 to 12 yr.	85% complete recovery, all cases were symptomatically well, 5 showed albuminuria attributable to nephritis.
Aldrich[3]	1931	129	1 to 10 yr.	93% recovered or convalescent, 0.8% clinically ill, 6.2% died in acute illness.
Tallerman[15]	1932	25	3 yr.	67% recovered.
McPhee, Kaye[16]	1932	48	----------	Both adults and children. 14.6% chronic.
Murphy, et al.[17]	1934	94	----------	Both adults and children. 27% mortality. 3 of 12 children developed chronic nephritis.
Folkers[18]	1935	68	3 yr.	Over-all mortality 14.7%, 4 cases died of chronic nephritis.
Richter[19]	1936	77	1 to 19 yr., average 8.7 yr.	80.5% recovered, 19.5% chronic nephritis. All adults, or over 12 yr. age.
Bierman[20]	1937	35	1 to 5 yr.	Less than 40% recovered.
Snoke[4]	1937	110	1 to 20 yr.	40% recovered, 13% dead, 47% "active."
Murphy, Rastetter[21]	1938	105*	2 to 14 yr.	39% recovered, 39% became chronic, and 12% died.
Snoke[22]	1939	102	1 to 11 yr.	74% recovered, 14% "active," 12% dead. Only 4 died of chronic nephritis.
Leavell, et al.[23]	1939	27	1 to 9 yr.	75% recovered.
Longcope[24]	1939	116	6 mo. to 14 yr.	Mixed group. Estimated 55 to 65% recovery.
Schwarz, et al.[25]	1940	120	1 to 16 yr., average 5 yr.	84% recovered.
Pittinos, et al.[26]	1941	32	1 to 12 yr.	97% recovered. 1 case, high blood pressure. Addis counts all normal.
Gachet[27]	1941	114	1 to 13 yr.	90.5% recovered.
Davis, Faber[28]	1945	102	----------	86.5% recovered, of survivors of initial stage.
Burke, Ross[29]	1947	90	Up to 2 yr.	93% recovered, 3% chronic nephritis.
Giles[30]	1947	218	Up to 7 yr.	73% recovered, 19% "latent."

*All patients under 30 years of age.

appeared in the literature in the last thirty years are highly variable, and seem in some instances to be contradictory. Morbidity and mortality figures are consistently higher in adults than in children. The percentages for children range from those reported by Snoke,[4] with 63 per cent combined morbidity and mortality, to those of Aldrich[5] who reported almost 100 per cent recovery of those children who survived the acute illness.

An exhaustive review of the literature is not indicated here, but reference is made in Table I to some of the frequently quoted reports to illustrate the wide divergence of results by several investigators. It may be noted that the results of two studies by the same observer[4, 22] are significantly contradictory.

TECHNIQUE AND SCOPE OF STUDY

The hospital and clinic records of approximately 200 children with the diagnosis of acute glomerulonephritis between 1917 and 1932 were carefully screened. Diagnostic criteria as described by Aldrich[32] were employed. These consist of hemorrhagic urine, antecedent or concomitant febrile infection, albuminuria, and cylindruria. Approximately seventy cases were thus rejected for various reasons, including, of course, death in the acute stage, incomplete record, and inadequate clinic follow-up. Approximately 130 cases were selected which could be classified unequivocally as acute hemorrhagic glomerulonephritis.

Tracer letters were sent to the last known address of these patients. In addition, an effort was made to locate the parents of the patients who were still listed in the telephone directory. When it is remembered that none of these records was less than twenty years old, that the series comprised patients of low economic level, a relatively migratory group, and that presuming none has died from any cause, all are now adults, it may be understood that the percentage of replies must be relatively small. Such was the case, and a total of twenty-seven patients were traced. Of the letters which were unanswered, approximately 95 per cent were returned unopened by the post office. Consequently, it is felt that the individuals who responded constitute a random sampling of the total number to whom letters were sent. The wording of the letter, which emphasized the importance to the patient of undergoing a simple examination, constituted a stronger stimulus to respond to those patients who might have had any illness even remotely associated with the urinary tract. Hence, it may be concluded that the half-dozen patients who presumably received the letter and who did not respond took no action because they judged it an unnecessary inconvenience.

Twenty-six of the patients (one had died) were asked routine questions regarding their memory of the original illness, either by personal memory or by parental recollection; serious interval illnesses; recurrences of specific kidney trouble; high blood pressure; major surgical operations; military service and life insurance examinations; number of pregnancies; and reports of physical examinations and urine analyses performed by their family physicians. Results of the queries are summarized in Table II.

Blood pressure recordings were obtained of seventeen patients. Record-

TABLE II. SUMMARY OF HISTORIES OF TWENTY-SEVEN PATIENTS WITH ACUTE GLOMERULONEPHRITIS BETWEEN AGE 2 AND 12 YEARS, PRESENT AGES BETWEEN 26 AND 41 YEARS

INIT.	BIRTH DATE	HOSPITAL DATE	AGE AT ONSET	AGE NOW	YEARS SINCE ONSET	SEX	ILLNESS WITH ACUTE NEPHRITIS	MILITARY SERVICE	PREGNANCIES	ILLNESS SINCE ADMISSION	BLOOD PRESSURE	URINE EXAMINATION
P. Z.	1912	1919	7	38	31	M	Otitis media	No	-------	None	Normal	Normal
F. B.	1918	1920	2	32	30	M	Otitis media, cervical adenitis	Yes	-------	None	Normal	Normal
R. G.	1908	1919	11	Died	--	M	Upper respiratory infection Mental defective	No	-------	----	----	----
H. K.	1921	1927	6	29	23	M	Acute tonsillitis	Yes	-------	None	Normal	Normal
L. W.	1921	1927	6	29	23	F	Pneumonia, tonsillitis	No	No	None	Not known	None
M. S.	1922	1924	2	28	26	F	Bronchopneumonia	No	2	None	Normal	Normal
C. R.	1919	1922	3	31	28	F	Acute pharyngitis, pertussis	No	Yes	Hysterectomy	Normal	Normal
M. P.	1922	1926	4	28	24	F	Otitis media	No	No	None	Not known	Not known
B. B.	1918	1926	8	32	24	M	Acute pharyngitis	Yes	-------	None	Normal	Normal
E. C.	1919	1931	12	31	19	F	No history	No	2	Urethritis	Normal	Neg. urethritis
P. M.	1916	1928	12	34	22	M	No history	Yes	-------	Asthma	Normal	Normal
E. P.	1923	1929	6	27	21	M	Acute tonsililtis	Yes	-------	None	Not known	Not known
G. C.	1919	1930	11	31	20	F	Scarlet fever	No	Yes	None	Slightly high	Normal
S. G.	1920	1930	10	30	20	M	Scarlet fever	Yes	-------	Rheumatic fever	Normal	Normal
R. R.	1924	1930	6	26	20	M	Acute pharyngitis, bronchitis	Yes	-------	None	Normal	Normal
B. J.	1919	1929	10	32	22	F	Upper respiratory infection Convulsions	No	No	None	Normal	Normal
B. P.	1918	1929	11	32	21	F	Acute pharyngitis	No	No	None	Normal	Normal
E. K.	1912	1924	12	39	27	F	Tonsillitis	No	No	Hysterectomy	Normal	Normal
J. K.	1916	1924	8	35	27	M	Acute pharyngitis	No	-------	None	Normal	Normal
M. S.	1919	1926	7	32	25	F	Febrile infection	No	2	Uterine "cyst"	Low	Normal
J. G.	1921	1927	6	30	24	M	Otitis media, cervical adenitis	Yes	-------	Pneumonia Scarlet fever	Normal	Normal
H. H.	1912	1918	6	38	32	M	Scarlet fever	Yes	-------	None	Normal	Normal
R. C.	1918	1924	6	33	27	F	Upper respiratory infection	No	No	Scarlet fever Mastoidectomy	Normal	Normal
I. B.	1909	1918	9	41	32	F	Convulsions, fever	No	2 cesarean sections	None	Normal	Normal
R. S.	1920	1922	2	31	29	M	Bronchitis	Yes	-------	None	Normal	Normal
B. P.	1925	1929	4	26	22	F	Mastoiditis	No	2	None	Normal	Normal
F. C.	1913	1917	4	37	33	F	No history	No	2	Radical mastectomy	Normal	Normal

ings of five others were reported by the patients or by their family physicians.

Quantitative and qualitative urinary sediment examinations by the new method of Addis[33] were performed on the urine of sixteen patients, and routine urinalyses were done on untimed specimens from three others. Leniency was allowed to influence the quantitative counts; for example, if the examiner was in doubt of the origin of a cell which might conceivably be a leukocyte or a tubule cell, it was recorded positively. Female patients were asked to collect clean voided specimens. Catheterized specimens, of course, are preferred, but it was not deemed practical nor, understandably, were the patients receptive to the procedure. Results are recorded in Table III.

TABLE III. BLOOD PRESSURE RECORDINGS, HELLER URINARY ALBUMIN TESTS, AND QUANTITATIVE (ADDIS) AND ROUTINE URINALYSES OF NINETEEN ADULTS WHO HAD ACUTE GLOMERULONEPHRITIS IN CHILDHOOD

INIT.	BLOOD PRESSURE	HELLER TEST	ADDIS COUNT (24-HOUR URINE)		
			ERYTHROCYTES	LEUKOCYTES AND EPITHELIAL CELLS	CASTS
I. B.*	130/80	Neg.	1,000,000	500,000	0
E. K.*	120/80	Neg.	1,000,000	3,000,000	0
L. W.*	92/68	Neg.	0	1,000,000	25,000
M. S.*	122/78	Neg.	2,000,000	750,000	0
B. J.*	132/87	Neg.	0	4,000,000	200,000
R. C.*	110/70	Neg.	500,000	1,000,000	0
M. S.*	110/80	Neg.	0	4,000,000	0
B. P.*	132/92	Neg.	0	2,000,000	0
H. K.†	125/85	Neg.	0	2,000,000	25,000
J. G.†	115/75	Neg.	500,000	1,000,000	25,000
H. H.†	Not taken	Neg.	0	1,000,000	0
P. M.†	110/70	Neg.	1,000,000	2,000,000	0
S. G.†	102/70	Neg.	0	500,000	0
J. K.†	104/62	Neg.	1,000,000	2,000,000	50,000
P. Z.†	124/84	Neg.	0	0	25,000
B. B.†	114/80	Neg.	0	1,000,000	25,000
C. R.*‡	114/75	Neg.	0	1/hpf	0
G. C.*‡	122/78	Neg.	0	0	0
R. R.†‡	Not taken	Neg.	0	4/lpf	0

*Females, uncatheterized.
†Males.
‡Routine urinalysis.

RESULTS

Twenty-six patients are alive, one is dead. The cause of death of this patient, a mental defective and epileptic, reported by the Dixon State Hospital, was pulmonary tuberculosis. Unfortunately no autopsy was performed.

The average age of the twenty-six patients at the time of illness was 7 years. The youngest child at time of illness was aged 2, the oldest aged 12. The average age now is 32 years. The oldest patient is now 41, the youngest 26. The average time elapsed since hospitalization for acute illness is twenty-five years. The smallest number of years since illness in any case was nineteen, and the greatest, thirty-three. The group comprised twelve males, ten of whom were in military service in World War II, and fourteen females, eight of whom have had one or more children. None of these women reported abnormal urinalyses, high blood pressure, or toxemia of pregnancy. Twenty-four of the group had recorded histories of antecedent or

concomitant infection. All patients showed grossly or microscopically hemorrhagic urine at the time of illness. Seventeen patients reported no serious illness since the attack of acute nephritis. The remaining nine patients reported serious illnesses or operations, only one of which was directly related to the urinary tract (see Table II). Two patients had scarlet fever several years after acute nephritis, with uneventful recoveries.

The blood pressure was reported as "normal" by twenty-one patients, "unknown" by three, "low" by one, and "slightly high" by one. This was checked and found to be normal. The urine examinations since illness were reported as "normal" by twenty-two patients, "not done" by three, and "normal" except for a recent attack of urethritis by one patient. This was confirmed by the physician who treated her.

All blood pressures of seventeen patients were within normal limits; the highest systolic pressure was 132, the highest diastolic was 92. Of the remaining nine patients, five reported normal readings by their family physicians, or the reports were obtained directly from the latter. Four were not available for readings, and had had no blood pressure recorded within recent years.

It is significant that a large number of this group had no knowledge of their illness in childhood or were aware only that they had been hospitalized in childhood because of an illness of unknown nature. This observation emphasizes the fact that many adults present erroneous histories with regard to previous renal disease, which impairs the validity of statistical reports in the literature.

The Heller test for urine albumin was negative in all nineteen specimens tested. The qualitative examination of the urinary sediment of sixteen patients revealed no significant abnormalities. The quantitative sediment counts of the same sixteen patients cannot, in any case except one, be interpreted as an indication of latent or chronic nephritis. This case, B. J., a female, had a cast count of 200,000 and an epithelial cell and leukocyte count of 4,000,000. The qualitative examination was normal. No erythrocytes were found. She is clinically well now, has had no serious illness, and the blood pressure is 132/87. It is highly questionable that this patient could be classified justifiably as a case of latent or chronic nephritis.

While some criticism may be justified regarding my figures when compared with the normal quantitative sediment count figures determined by Addis,[33] it must be remembered that an effort was made to count all doubtful abnormal elements; further, that a maximum of four unit volume counts were made on the sediment of the majority of patients, and that females were not catheterized.

The urine of three patients, due to errors in following instructions, was not suitable for accurate Addis counts, and routine urinalyses only were done. These were negative. Urine specimens were not obtained from seven patients, because of refusal to cooperate or inability to come to the hospital.

DISCUSSION

The references in Table I represent the major portion of studies undertaken to determine the prognosis of acute glomerulonephritis in childhood. No reports were found of follow-up

studies conducted for an average time of more than ten years, with the exception of that of Ernberg[34] in 1911. He studied forty adults who had had acute nephritis before age 15 years, and found normal urines in all, and sixteen adults who had had acute nephritis between ages 15 and 30 years, all of whom were normal except four.

Schwarz, Kohn, and Weiner[25] noted that "much longer periods of observation are necessary to establish the relationship of the nephritis of adult life to an attack in childhood. It is notoriously difficult to obtain a history of acute nephritis in childhood from an adult 40 to 60 years old." This observation is notably illustrated in the present study, even though the average age of this group is now only 32 years.

The question of whether acute nephritis suffered in childhood is frequently the onset of a latent stage which is revealed as chronic nephritis in adulthood is still unsettled. The truth has been unusually elusive primarily because there is a dearth of chronologic pathological studies of acute nephritis, and because there is much inconsistency between the pathological and clinical characteristics of the disease. Moreover, we are still unaware of the true nature of the changes which occur in the kidney during an attack of acute nephritis.

Secondarily, we are handicapped by the patient himself, who so often gives an inaccurate history. Some workers[1, 17, 21, 33, 35] believe that there are many more cases of acute nephritis than those which come to the attention of physicians, the implication being that these subclinical cases contribute substantially to the incidence of chronic nephritis in which no record of an acute attack may be found. Others[3, 5, 13, 24, 36, 38] present substantial evidence that chronic nephritis, with rare exception, is not preceded by an acute attack.

There is no question that the regenerative capacity of the kidney in infancy and childhood is greater than in the adult, which may partially explain the difference in morbidity figures for adults and children. However, it sheds no light on the question of why the patient who has suffered an initial insult to the kidneys develops chronic nephritis, which over a period of years or even decades gradually results in almost total destruction of the renal parenchyma.

It has been the observation in this clinic that almost 100 per cent of children with acute nephritis who survive the initial illness recover completely.[37] Further, in no instance in which the urine has cleared completely (by routine urinalysis) has a child been observed to develop chronic nephritis. The rare instance in which chronic nephritis has been observed to follow acute nephritis has been characterized by a continuous and rapid downhill course. Conversely, chronic nephritis in children begins insidiously in the majority of cases with no history of antecedent or concomitant infection.[38] In several instances, there has been no recognizable illness of any sort in very young children. It is indeed difficult to assume that these children have at some time in their short lives suffered an attack of subclinical acute nephritis.

We have noted[38] that in recent years the percentage of admissions to the clinic and hospital for acute nephritis has dropped significantly, the reason for which one may speculate is the reduction in number and severity of

hemolytic streptococcal infections by the widespread use of bacteriostatic and antibiotic drugs. However, in the same period there has been some increase in the case percentage of chronic nephritis. No conclusions, of course, are justified at this time, but if the trend continues it may be significant.

Loeb and associates[31] reported ten patients with healed acute nephritis observed for four years who had recurrent hemolytic streptococcal infections, two of whom had recurrent hematuria, and none of whom developed chronic progressive kidney disease. They state that "no case of healed acute glomerulonephritis has subsequently been observed to develop the chronic form of the disease."

Bradley and co-workers[1] studied twenty patients during the acute attack, subsequent healed period, and following a later infection with group A hemolytic streptococcus. Eighteen of twenty patients showed no urinary abnormality and none developed chronic nephritis.

The burden of proof, it seems, must rest upon those who assume that cases of subclinical acute nephritis occur in significant numbers to explain the corresponding incidence of chronic nephritis. It is not within the scope of this report to attempt to disprove such a concept. The results of the present study and the experience of this clinic are presented as evidence that acute nephritis in children is a benign disease which rarely is the initiating factor in the onset of chronic nephritis, either in childhood or in the adult life of the individual.

It is suggested that further studies of this type may offer a final solution with regard to the relationship between acute and chronic nephritis. With the accumulation of accurate hospital and clinic records, it may be possible to follow cases from the time of illness to death, and to correlate the complete history of these patients with autopsy reports in sufficient numbers to arrive at a final answer to the problem.

SUMMARY

Interval histories, blood pressures, and urinalyses of twenty-six adults who suffered acute glomerulonephritis in childhood were obtained to determine their present status.

The smallest number of years since illness in any case was nineteen, the greatest, thirty-two. The oldest patient is now 41, the youngest, 26 years of age. None of this group had any illness referable to the urinary system at the time of the study.

Blood pressure was reported normal by twenty-two patients, slightly high by one. The latter was found to be normal. Urine examinations since original illness were reported normal by twenty-two patients, and one patient had had a recent attack of urethritis.

The blood pressure of seventeen of the group was obtained and found to be normal in all. The Heller test for urine albumin was negative in all nineteen specimens tested. Qualitative and quantitative examinations of the urinary sediment (Addis) of sixteen patients were done, revealing no significant abnormality.

Significance of the results is discussed.

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FACIAL ASYMMETRY IN THE NEWBORN INFANT; ITS RELATION TO CONGENITAL CRANIAL OSTEOPOROSIS (CRANIOTABES) AND INFANT'S BIRTH ORDER

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THIS study of 1,425 newborn infants in Los Angeles and Mexico City, supplementing an earlier investigation[2, 17] of congenital cranial osteoporosis, known also as congenital craniotabes,* provides additional data on its relationship to facial asymmetry in the newborn infant.

The term facial asymmetry is used in this paper to denote that type of asymmetry, often encountered in the newborn infant, which, according to Parmelee,[15, 16] is due to the sustained intrauterine postural pressure effects of a juxtaposed shoulder and jaw. The juxtaposition is manifested by an indentation on the affected side of the infant's neck associated with a characteristic malocclusion consisting in an overlapping of the alveolar ridges on the affected side and a gaping on the other. The term facial asymmetry refers throughout the paper to this congenital postural form.

The earlier results indicated that such facial asymmetry was far more frequent among infants with congenital craniotabes than among infants with firm, well-calcified skulls.[17] This suggested that intrauterine pressure is not the sole etiological factor in facial asymmetry.

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*The term "congenital craniotabes" is used in this paper as a descriptive clinical term for the condition of congenital softness of the skull in the newborn infant, whereas the term "congenital cranial osteoporosis" is used in reference to its underlying pathology.[2]

The frequent association of facial asymmetry with congenital craniotabes is of practical rather than merely academic interest for the following reasons:

1. Certain permanent head and facial asymmetries and dentofacial deformities, which frequently have their onset in early infancy and may be severe enough to be of orthodontic significance, have been ascribed to an osteoporosis of the cranial and facial bones at birth.[11, 12]

2. Congenital craniotabes may be a valuable diagnostic sign of osteoporotic cranial and facial bones at birth, since clinical evidence indicates that it is a sign not merely of a localized deficient calcification but also of a more generalized osteoporotic process (Finola and associates,[8] Maxwell and coworkers,[13] Reiss and Boder,[17] Toverud,[19] and others).

3. The degree of calcification of the infant's cranial bones, as well as of general bony calcification, may be influenced by prenatal measures, such as maternal exposure to sun[2, 3, 17] or supplemental administration of dicalcium mental administration of dicalcium phosphate with vitamin D (Brehm,[4] Finola and associates,[8] and others).

Since congenital cranial osteoporosis may be a factor predisposing to congenital facial asymmetry, the question arises whether if uncorrected, it might not also be a factor predisposing to postnatal head and facial asymmetries

or dentofacial deformities. Thus further knowledge on the etiology of facial asymmetry in the newborn infant may be of practical pediatric and orthodontic interest.

MATERIAL AND METHODS OF INVESTIGATION

This study supplements the earlier investigation[2, 17] of 875 newborn infants from the obstetric wards of the Los Angeles County General Hospital, by further analysis of the original data. In addition it reports observations on a new series of 550 infants from the obstetric wards of two municipal hospitals in Mexico City, the "Hospital General" and "Maternidad de las Lomas," obtained in the summer of 1941 and 1942. The present study is thus based on a total of 1,425 infants. The type of material, methods of investigation, and criteria for the classification of infants into the various skull-type categories are essentially the same as in the earlier reports.[2, 17]

Briefly, infants were arbitrarily classified into three groups: (1) Infants with "hard" skulls showed no yielding or compressibility of bone on light or moderate palpation; (2) those with "soft" skulls showed a definite yielding or softness (either "ping-pong" or "parchment" in type) of more than one-half the bony vertex; and (3) those with "transitional" skulls showed all lesser degrees of bony softness no matter how small the area of involvement. Thus the soft skull group with the marked forms of cranial softness, and the transitional with the slight or moderate forms, together constitute the "osteoporotic" skull group.

The contention that such classification based wholly upon clinical diagnostic criteria must be arbitrary is admitted. Nevertheless, it is as accurate and objective as is possible in a purely clinical investigation, since craniotabes can be much better appreciated by palpation than by roentgenographic visualization.[5]

TABLE I. DISTRIBUTION OF FACIAL ASYMMETRY AMONG HARD AND OSTEOPOROTIC SKULL GROUPS

	TOTAL		TYPE OF SKULL							
			HARD		TRANSITIONAL		SOFT		TRANSITIONAL PLUS SOFT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Total in the different skull type groups	794	100.0	536	100.0	199	100.0	59	100.0	258	100.0
Distribution of facial asymmetry										
Present	54	6.8	22	4.1	20	10.1	12	20.3	32	12.4
Absent	740	93.2	514	95.9	179	89.9	47	79.7	226	87.6

RESULTS OF THE INVESTIGATION*

As in the previous studies, the reliability of the results obtained was determined by the application of the critical ratio and the Chi square tests.†

The earlier results reproduced in Table I indicated that facial asymmetry was almost five times as frequent in infants with soft skulls, and fully twice as frequent in those with transitional skulls, as in those with hard

*Numerous tables pertaining to the results of the investigation have been omitted. They may be obtained from the author.

†The term "significant" is used to indicate differences having critical ratio values of 2.57 or more, and in the Chi square test a P value less than 0.05; "suggestive" having critical ratio values between 1.96 and 2.57; and "non-significant" having critical ratio value less than 1.96 and a P value of 0.05 or more.[3, 9, 18]

skulls, the differences being significant both according to the critical ratio and the Chi square test (C. R. values: 3.08 and 3.77. P value: 0.01-).

Additional analysis of the original data consisted in investigating the incidence of facial asymmetry in relation to maternal parity and infant's birth order. It was argued that if such facial asymmetry is actually the result of sustained intrauterine postural pressure effects,[15, 16] it should occur with greater frequency among offspring of primiparas since they are subject to greater intrauterine pressure than those of multiparas (Davison,[6] Abels and Karplus,[1] and others). Table II and Fig. 1 show that facial asymmetry was actually twice as frequent among the offspring of primiparas as among those of multiparas, the difference being highly suggestive according to the critical ratio (C. R. value: 2.34), and significant according to the Chi square test.

This higher incidence of facial asymmetry in first-born infants was observed in the hard as well as in the osteoporotic skull groups (Table II and Fig. 1) and is, therefore, unrelated to the coexisting higher incidence of congenital craniotabes among first-born infants. Similarly, the higher incidence of facial asymmetry among infants with osteoporotic skulls was observed among offspring of primiparas as well as those of multiparas (Table II, Fig. 1) and is, therefore, unrelated to parity. The fact that facial asymmetry can occur independently of both primiparity and congenital cranial osteoporosis (Table II) appears to indicate that the pressure effects of sustained intrauterine posture may alone be responsible for its development as claimed by Parmelee.[15, 16] The more frequent occurrence of facial asymmetry among first-born infants and those with congenital cranial osteoporosis nevertheless indicates that increased intrauterine pressure or increased bony plasticity are also important causative factors.

The relationship of facial asymmetry to congenital craniotabes as well as to maternal parity was subsequently corroborated in the investigation conducted in Mexico City. In the new series of 535 newborn infants, of which 422 or 78.9 per cent belonged to the hard-skull group and 113 or 21.1 per cent to the osteoporotic, the total incidence

TABLE II. DISTRIBUTION OF FACIAL ASYMMETRY IN RELATION TO MATERNAL PARITY AMONG INFANTS WITH HARD AND OSTEOPOROTIC SKULLS

	TOTAL		TYPE OF SKULL							
			HARD		TRANSITIONAL		SOFT		TRANSITIONAL PLUS SOFT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Total primiparas	256	100.0	161	100.0	76	100.0	19	100.0	95	100.0
Distribution of facial asymmetry										
Present	26	10.2	8	5.0	13	17.1	5	26.3	18	18.9
Absent	230	89.8	153	95.0	63	82.9	14	73.7	77	81.1
Total multiparas	496	100.0	342	100.0	114	100.0	40	100.0	154	100.0
Distribution of facial asymmetry										
Present	26	5.2	13	3.8	8	7.0	5	12.5	13	8.4
Absent	470	94.8	329	96.2	106	93.0	35	87.5	141	91.6

of facial asymmetry was 3.2 per cent. Thus the incidence of both facial asymmetry and craniotabes was lower in the Mexico City than in the Los Angeles series.[2, 3, 17] The new observations also revealed that facial asymmetry was twice as frequent in infants with osteoporotic skulls (6.2 per cent) as in those with hard skulls (3.3 per cent). Its incidence among 180 offspring of primiparas was 8.3 per cent as compared with 1.7 per cent among 355 offspring of multiparas, the difference being significant with a critical ratio value of 3.06.

Further analysis of the Los Angeles data also indicated that the incidence of facial asymmetry showed a tendency to decrease as the infant's birth order increased. No statistical analysis of these results was made because of the small number of observations.

There are no similar data available in the literature for comparison.

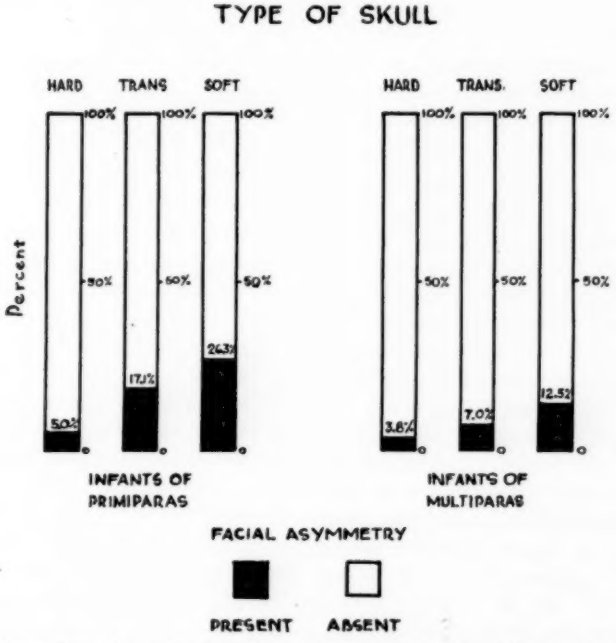

Fig. 1.—Incidence of facial asymmetry in relation to maternal parity among infants with hard and osteoporotic skulls.

The higher incidence of facial asymmetry among offspring of primiparas supports the theory of mechanical-postural causation proposed by Parmelee,[15, 16] since, as indicated above, infants of primiparas are subject to greater intrauterine pressure than those of multiparas.[1, 6] However, the higher incidence of facial asymmetry among infants with craniotabes, unre-

COMMENT

The results of this study will be discussed in the light of the previous data[2, 17] and the more recent clinical evidence.

lated to parity, clearly suggests osteoporotic involvement of the facial bones as an additional causative factor. This finding, like the higher incidence of conically shaped chests among newborn infants with osteoporotic skulls,[17] is consistent with Toverud's[19] concept of the generalized nature of congenital cranial osteoporosis. Facial asymmetry manifesting the juxtaposition of shoulder and jaw appears, then, to be caused largely by intrauterine postural pressure effects[15, 16] as the primary factor, with increased plasticity of facial bones due to congenital osteoporosis as an important contributory factor.

The "flat head, soft chest" syndrome[12] and certain postural head asymmetries and dentofacial deformities,[11] which frequently have their onset in early infancy, have also been ascribed to an osteoporosis of the respective bones at birth. The higher incidence of facial asymmetry and conically shaped chest[16] among newborn infants with osteoporotic skulls[17] supports to some extent the theories of Hess and Greene.[11, 12] In other words, since congenital cranial osteoporosis may be a factor predisposing to facial asymmetry in the newborn infant, it is readily conceivable that if uncorrected, it may also be a factor predisposing to early postnatal head and facial asymmetries.

Newer clinical evidence does, in fact, indicate that infants with congenital craniotabes are more susceptible to the head and facial asymmetries that may result from the sustained pressure effects of lying habitually on one side. In an adoption agency nursery ("The Cradle," Evanston, Ill.), where infants are kept under observation from about the second to the seventh or eighth week of life, Rosenstern noted that such postural head and facial asymmetries were far more frequent among infants with craniotabes than among those with firm, well-calcified skulls. Since these infants were first examined in the neonatal period, the craniotabes observed by Rosenstern is, undoubtedly, of the congenital type inasmuch as the so-called postnatal or rachitic craniotabes usually makes its first appearance when the infant is 3 or 4 months old (Eliot and Park,[7] Moore and Dennis,[14] and others). However, even postnatal craniotabes leads to postural pressure deformities, such as flattening of the occiput, or occipitoparietal flattening with asymmetry of the cranium in infants who habitually lie on one side.[5, 20]

Congenital cranial and facial osteoporosis may thus explain why head and facial asymmetries and even certain orthodontic deformities, frequently originating in early infancy,[11, 20] develop as a result of thumb-sucking, facial sleeping positions, and other sustained postural and pressure factors in some infants and not in others.

This study, supported by clinical evidence,[5, 11, 12, 18, 20] provides a new basis for investigating the etiological relationship of congenital cranial osteoporosis to the postnatal head asymmetries and dentofacial deformities that result from postural or pressure factors. Since congenital cranial osteoporosis may be open to prophylactic[2, 4, 8, 17, 19] as well as therapeutic measures, this problem assumes practical pediatric and orthodontic[11] importance.

On this basis the following routine for the newborn infant, described in greater detail in the earlier investigation,[2] suggests itself anew: (1) complete physical examination of all new-

born infants, and particularly of those with facial asymmetry, should include a systematic search for craniotabes; (2) in all cases of congenital craniotabes, measures should be taken to secure adequate calcification of the infant's cranial bones by correcting any vitamin D or calcium and phosphorus deficiencies that may exist, utilizing the earlier administration of vitamin D and the larger dosage standard in the management of the premature infant; (3) early postural measures to prevent flattening of the occiput, head and facial asymmetries, and dentofacial deformities should be taken for all infants with craniotabes who show a decided preference for a given head position.

SUMMARY

This study supplementing an earlier investigation presents additional observations on such facial asymmetry in the newborn infant as manifests the juxtaposition of shoulder and jaw in utero; also on the relationship of such facial asymmetry to congenital craniotabes.

This study now comprises a total of 1,425 nonselected, apparently full-term newborn infants of Los Angeles and Mexico City. It confirms the relationship of facial asymmetry in the newborn infant to congenital craniotabes, or clinically demonstrable congenital cranial osteoporosis, and establishes a relationship to the infant's birth order.

No published reports were found concerning the relationship of facial asymmetry to either of these factors. This study supports a broader clinical concept of facial asymmetry and of congenital craniotabes, and provides a new basis for investigating their etiological relationship to certain postnatally acquired head and facial asymmetries or dentofacial deformities. The systematic search for craniotabes is urged as part of the routine physical examination of all newborn infants, and particularly of those with facial asymmetry. A diagnostic and therapeutic routine for the newborn infant with both facial asymmetry and craniotabes, or craniotabes alone, is outlined.

CONCLUSIONS

1. Facial asymmetry in the newborn infant manifesting the juxtaposition of shoulder and jaw in utero shows a marked predilection for infants with craniotabes; also for offspring of primiparas.

2. The predilection of facial asymmetry for newborn infants of primiparas, as compared with those of multiparas, supports the theory of mechanical-postural causation proposed by Parmelee.

3. The predilection of facial asymmetry for newborn infants with craniotabes suggests osteoporotic involvement of the facial bones as an important contributory factor.

4. The frequent association of facial asymmetry and congenital craniotabes also supports the existing clinical evidence that infants with an osteoporosis of cranial and facial bones at birth may be more susceptible to such postnatal head and facial asymmetries and dentofacial deformities as have their onset in early infancy.

5. Since avitaminosis D during pregnancy may be responsible for the development of congenital cranial osteoporosis, the administration of vitamin D to the mother prenatally in order to insure normal calcification of the infant's cranial bones, has practical pediatric and even orthodontic impor-

tance, and should take its place alongside the now standard administration of vitamin D to the infant postnatally.

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THE TREATMENT OF GROWTH FAILURE IN ALEUT SCHOOL CHILDREN

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THE growth and development of children is a highly complex phenomenon the analysis of which has been simplified by Wetzel[1] in his Grid for Evaluating Physical Fitness. The Grid was developed over a period of years. It is based upon the records of growth and development of 4,500,000 children from all parts of the world, as reported in more than 400 published papers.[2] Its application to Aleut children was first confirmed by Wilde[3] and later by Garns.[4]

Pure, crystalline vitamin B_{12} was first prepared by Rickes and associates.[5] Its effect as an essential nutrient for growth was first demonstrated in the case of microorganisms by Shorb.[6] Vitamin B_{12} has since been reported as a growth factor for chicks,[7-13] rats,[14-18] pigs,[19-21] and mice.[22]

Growth failure in school children as a manifestation of functional deficiency of vitamin B_{12} and its favorable response to oral therapy was first reported by Wetzel and collaborators.[23] A favorable effect of vitamin B_{12} on the growth of children has also been noted by Chow[24] and by O'Neil and Lombardo.[25]

The present study was undertaken to determine the effect of a nutritional supplement (Infa-Concemin with B_{12} Activity†) upon the growth and development of retarded Aleut school children. It was selected since it contains, in addition to vitamin B_{12}, a number of the established vitamins. Each cubic centimeter of this formula contains:

Thiamine hydrochloride	0.8 mg.
Riboflavin	0.8 mg.
Niacinamide	5.0 mg.
Pyridoxine hydrochloride	0.5 mg.
Rice bran extract (supplies additional B-complex factors)	67.5 mg.
Ferrous sulfate	37.5 mg.
Vitamin B_{12} activity (contributed by a special extract of liver and vitamin B_{12} in streptomyces fermentation extractives)	2.0 μg.

The test subjects consisted of four girls and five boys ranging in age from 10 to 14 years. Prior to treatment the Grid records were available for five years in the case of eight subjects and three years in the other. The subjects were selected because of growth failure,[2, 18] particularly because of a slowdown in the rate of development. Therapy with Infa-Concemin with B_{12} was started on Sept. 15, 1950. It was administered in 5 c.c. doses by the schoolteacher daily from Monday through Thursday and 10 c.c. each Friday. No medication was given during the week end since an accurate record of the dosage could only be obtained by administration in school.

Prior to medication, each of the subjects had been receiving for a period of four years one Pan-Concemin* tab-

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†Infa-Concemin is the trade-mark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, from whom supplies were generously provided.

*Pan-Concemin is the trade-mark of The Wm. S. Merrell Company, Cincinnati 15, Ohio.

let daily in school, each such tablet containing:

Vitamin A	5,000 U.S.P. Units
Vitamin D	800 U.S.P. Units
Thiamine hydrochloride	3 mg.
Riboflavin	2 mg.
Ascorbic acid	50 mg.
Niacinamide	20 mg.
Calcium *d*-pantothenate	2 mg.
Pyridoxine hydrochloride	1 mg.

It was felt that the test subjects had been receiving the usual, established vitamins daily during previous school years. Other conditions were relatively unchanged. Any improvement in the rate of growth and development in the treated children would probably be due to the added growth-stimulating effect of vitamin B_{12}.

This study is unique in that the entire economy of the people on St. Paul Island is regimented and standardized. These Aleuts are all wards of the United States Government. As such they received besides housing a basic food issue, clothing, a variable salary, and a variable bonus at the end of each sealing season. The question of inadequacy of the food supply must be considered but this has been eliminated.

These Aleuts live in standard houses of which there are three types, all very similar. They are all heated by means of a kitchen range which is fired with wood and coal. The weekly food issue ranges from 3,000 to 4,000 calories per person per day. It is high in fats and carbohydrates but relatively low in protein. The amount of canned milk given is essentially as much as the families can consume. This food issue is supplemented by purchases at the community canteen and further supplemented by hunting and fishing.

The Aleuts have retained their aboriginal hunting and fishing rights and have the use of these despite any restrictions placed upon others. They are able to secure seal meat as they desire during the sealing season which lasts from the middle of June to the first of August. A few of the more diligent salt seal meat for the winter or freeze it in the food locker. Thus, for all those desiring it a plentiful supply of food is available, but it does not follow that all foodstuffs necessarily reach the table in a palatable, edible form.

In the nine children selected for study because of continuing growth failure, factors of ill health had to be ruled out. Physical examination revealed that none of them had any demonstrable disease. There was no cardiac disease in the group. Tuberculosis was ruled out in all of them by 14 x 17 chest films which were taken in 1948 and again in 1951. Four of the nine had negative reactions to P.P.D. in 1946 and 1948; the four negative reactors were vaccinated with BCG in 1948. All of them have been successfully vaccinated against smallpox and immunized against pertussis, tetanus, and diphtheria. None of the immunizations were given during this study.

The milder contagious diseases, such as chicken pox, measles, mumps, are a negative factor on the island. The common cold strikes when a ship arrives with someone aboard who has a cold. A small epidemic of colds follows which disappears very shortly. All of these above-mentioned factors are more or less under the control of the medical officer, and therefore the lives of Aleutian children are very well standardized.

There are other factors, however, which influence growth and cannot be controlled. One of these is discipline

TABLE I. EFFECT OF INFA-CONCEMIN WITH VITAMIN B_{12} ON RATE OF GROWTH IN RETARDED CHILDREN

PATIENT	DATE	WEIGHT (LB.)	HEIGHT (IN.)	DEVELOPMENTAL LEVEL*	DATE	WEIGHT (LB.)	HEIGHT (IN.)	DEVELOPMENTAL LEVEL*	PRE-TREATMENT GROWTH RATE (LEVEL/MONTH)	DATE	WEIGHT (LB.)	HEIGHT (IN.)	DEVELOPMENTAL LEVEL*	TREATMENT GROWTH RATE (LEVEL/MONTH)	CHANGE IN GROWTH RATE DURING TREATMENT (IN LEVELS/MONTH)	PERCENTAGE CHANGE IN GROWTH RATE DURING TREATMENT
K. J.	1/10/49	74	53½	95.8	9/12/50	79½	56⅞	104.7	0.44	4/10/51	83¼	57⅜	109.3	0.65	+0.21	+47.7
A. H.	3/15/49	51	46⅛	55.8	9/13/50	55½	48½	65.5	0.57	4/10/51	60	49½	73.5	1.14	+0.57	+100.0
N. G.	9/27/48	57	48½	68.0	9/12/50	65½	51½	83.1	0.63	4/10/51	70½	53	91.0	1.13	+0.50	+79.3
I. M.	9/27/48	41	44¼	33.9	9/13/50	47½	47½	50.1	0.67	4/ 9/51	52¼	48¾	60.0	1.41	+0.74	+110.4
A. K.	9/27/48	63	51½	79.4	9/13/50	74	55½	97.1	0.73	4/ 9/51	77	56⅜	101.4	0.47	−0.26	−35.7
P. K.	9/27/48	55	50¼	65.8	9/11/50	65	53⅜	83.7	0.74	4/10/51	70	55¼	91.7	1.14	+0.40	+54.0
V. S.	9/27/48	57	49½	68.6	9/11/50	67½	53	86.9	0.76	4/10/51	73	54½	95.2	1.18	+0.42	+55.2
X. K.	9/27/48	49¾	49⅝	55.9	9/12/50	60½	53½	76.9	0.87	4/10/51	63	55⅛	81.8	0.70	−0.17	−19.5
J. O.	9/27/48	50	48⅝	55.7	9/12/50	63	52⅝	80.1	1.01	4/10/51	69	54	89.6	1.35	+0.34	+33.9

*The developmental level can be calculated from the formula: $D = (q_y - b_o) \sin \alpha + q_x \cos \alpha$. (Medical Physics, p. 533, Year Book Publishers, 1944.)

of the children by the parents. Discipline involves the matter of sufficient food served at the proper time, the proper amount of sleep, cleanliness, and a happy home life. Sleep is particularly variable among Aleut children. Failure to obtain it at night is evident from a common tendency to fall asleep throughout the entire day in school.

The results of nutritional supplementation, employing Infa-Concemin with B_{12} were highly gratifying, as indicated in Tables I and II.

A period of eighteen to twenty-four months before the new supplement was employed was used as a control. During the period of treatment there was a striking increase in the rate of growth in seven of the nine subjects, as measured in Grid levels per month.[26] The two remaining cases (A. K. and X. K.) illustrate that in some instances nutritional supplementation will not overcome other factors, such as lack of food, lack of sleep, lack of discipline, and various emotional disturbances. Of particular interest, however, is the fact that the growth rate in terms of developmental levels per month was restored, from a control rate of 0.71 before treatment to 1.02 levels per month. This is a value that coincides with the standard rate of 1 level per month characteristic of all healthy children of school age in any part of the world.[26] This is an increase in the rate of growth and development of 43.6 per cent. In considering only the seven children who responded, the growth rate during the test period was 1.14 levels per month. This indicates that the growth failure had been stopped and that the previous lag was being corrected. The increase in the rate of growth and development is 65.2 per cent. These findings are consistent with the reports of Wetzel and associates,[23] indicating that in some children growth failure occurs as a manifestation of functional deficiency of vitamin B_{12} and that it may be corrected by oral administration of vitamin B_{12}. Such was the case in seven of the nine children here reported.

TABLE II. SUMMARY OF GROWTH RESPONSE TO INFA-CONCEMIN WITH VITAMIN B_{12}

	AVERAGE PRE-TREATMENT RATE OF GROWTH (LEVELS/MONTH)	AVERAGE RATE OF GROWTH DURING TREATMENT (LEVELS/MONTH)	AVERAGE INCREASE IN GROWTH RATE (LEVELS/MONTH)	PERCENTAGE CHANGE
Entire group (7 who responded; 2 who did not)	0.71	1.02	+0.31	+43.6
Group of responders (7 cases)	0.69	1.14	+0.45	+65.2

SUMMARY AND CONCLUSIONS

A series of nine Aleut school children suffering from retarded growth and development were treated with Infa-Concemin with B_{12}. In seven of these there was an average increase of 65.2 per cent in rate of growth during seven months of treatment as determined by the Wetzel Grid technique.

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THE USE OF BANTHINE BROMIDE* IN INFANTILE COLIC AND VOMITING

Preliminary Report of Fifty Cases

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THE medical management of infantile colic and pylorospasm in the newborn period has always been a difficult problem for the pediatrician. The transient and varied nature of these symptom complexes, especially infantile colic, increases the difficulty in solving the etiology and therapy.

With regard to colic, Brennemann[1] confessed "to no little bewilderment as to this elusive phenomenon." Among the theories of causation have been mentioned hunger and underfeeding, overfeeding and flatulence, imbalance of the autonomic nervous system leading to enterospasm, environmental disturbances, improper feeding technique, allergy, constitutional hypertonicity, and abdominal distention.[2-8] According to White,[4] colic is a vagogenic gastroenterospasm with the entire gastrointestinal tract often involved in the hypermotility. Recently, Levine and Bell[9] reported the successful application of the pacifier in the treatment of colic in infancy. These authors believe that the crying of colicky infants is due to an unsatisfied need for oral gratification. Levin,[10] in recording the rare occurrence of colic in institutions, suggests that some emotional factor may account for the higher incidence of colic in the private home, although keener observation might demonstrate more cases among institutionalized infants. Spock[11] emphasizes that the age period of 2 weeks through 3 months is one of heightened tension, when the infant has an avid appetite, cries more, and has greater difficulty in falling asleep. The common occurrence of colic in the late afternoon and in the evening suggests that fatigue may also be a factor in causation. Gesell and co-workers[12] refer to the increased irritability of the newborn age period and note that crying tends to occur prior to sleep, especially in the afternoon and evening. The various therapeutic regimes for alleviating colic have included antispasmodics, opiates, barbiturates, improved feeding technique, formula adjustments, pacifiers, and change in body position.[1-10, 13, 14]

Vomiting, like colic, is one of the most common symptoms in infancy,[8] and pylorospasm accounts for most of those cases where organic lesions like pyloric stenosis have been ruled out. Nelson[8] feels that the hyperactive or neurotic infant will vomit more readily. Regurgitation, with certain exceptions, is considered a natural occurrence during the newborn period. Anderson[2] has attributed vomiting to overdistention of the stomach by swallowed air, frequent feedings, improper clothing and handling, gastroenterospasm, and allergy. Drug therapy for vomiting has usually consisted of antispasmodics and barbiturates.[8, 15]

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*Supplied by a grant from the G. D. Searle & Co., Chicago, Ill.

PHARMACOLOGY OF BANTHINE BROMIDE

Banthine bromide is a new quaternary amine (beta-diethylaminoethyl xanthine-9-carboxylate methobromide). Longino and collaborators[16] introduced the clinical application of Banthine as the medical counterpart of vagotomy. During the past two years there have been numerous reports in the literature describing the successful application of Banthine in the therapy of duodenal ulcer.[17-26] Banthine is an anticholinergic drug that arrests or depresses the motility of the stomach, small intestine, and colon, and usually reduces the volume and free acid of the stomach secretions.[27-29] These effects are accomplished through an inhibition of the action of acetylcholine in the ganglions of the autonomic sympathetic and parasympathetic systems and in the postganglionic nerve endings of the parasympathetic system. After administration, the action of Banthine persists for two to six hours. Experiments on human beings indicated that Banthine has an antiparasympathicomimetic action, and is possibly more effective in decreasing intestinal contractions than tincture of belladonna.[30] The predominant action of Banthine is a parasympathetic neuro-effector blockade. According to Kern and associates,[31] Banthine is the only drug available today that has a prolonged inhibitory effect on human gastrointestinal motility. Grimson[27] suggested that a good anticholinergic drug, like Banthine, might be effective in the treatment of certain chronic colicky abdominal pains. In view of the pharmacologic actions of Banthine, the authors felt that this new drug was worthy of a trial in treating cases of infantile colic and vomiting.

METHOD OF STUDY

Banthine bromide was administered to fifty infants, ranging in age from 1 to 32 weeks. Twenty-five infants were between 1 and 4 weeks of age, and only four infants were above 2½ months of age. Sex distribution was almost equal, with twenty-six male and twenty-four female infants. The cases were divided into three groups, according to the most troublesome symptom; twenty-three infants had pure colic, twelve had vomiting, and fifteen had both colic and vomiting. Table I presents a detailed analysis of the fifty cases. The drug was usually administered in 5 mg. doses four times a day. Banthine is an extremely bitter-tasting drug which is difficult to disguise in a vehicle, but was apparently readily accepted by all the infants. It was dispensed in a 5 mg. dosage capsule, or in sterile water containing 5 mg. per teaspoonful. The dose was usually dispersed into a formula feeding.

TOXIC EFFECTS

In adults, toxic effects that have been noted are: excessive dryness of the mouth, urinary frequency and slowness of the urinary stream, some lack of visual accommodation, urinary retention in patients with benign prostatic hypertrophy, constipation, and tachycardia.[19, 25, 26] Benson and coworkers[32] recently tested the sensitivity, toxicity, and tolerated dosage of Banthine in children. Skin tests were performed on 415 cases, of which five had local erythematous reactions. Two children had systemic manifestations consisting of flushing, tachycardia, irritability, dryness of membranes, and pupillary dilatation. In eighty-five conjunctival tests, sixty-

TABLE I. INDIVIDUAL ANALYSIS OF FIFTY CASES OF INFANTILE COLIC AND PYLOROSPASM TREATED WITH BANTHINE

CASE	SEX	AGE	COLIC	VOMITING	PREVIOUS THERAPY	OCCURRENCE OF SYMPTOMS	TYPE FORMULA MILK	BANTHINE DOSAGE	DURATION OF THERAPY	RESULT
1. R.B.	F	8 mo.	0	***	Belladonna	P.C. for 2 mo.	Whole milk	5 mg. q.i.d.	3 wk.	Good
2. P.A.	M	1 mo.	***	***	Belladonna Phenobarbital	Day and night	Similac	5 mg. q.i.d.	1 mo.	Good
3. D.B.	M	1 mo.	0	***	None	P.C.	Similac	5 mg. q.i.d.	2 wk.	Good
4. H.J.	F	3 wk.	***	***	None	P.C.	Evap. milk	5 mg. q.i.d.	2 wk.	Mod. Good
5. D.J.	M	1 mo.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	3 wk.	Poor
6. E.C.	M	1 mo.	0	***	None	P.C.	Evap. milk	5 mg. q.i.d.	3 wk.	Poor
7. R.C.	M	4 mo.	0	***	Belladonna Phenobarbital	P.C.	Evap. milk	5 mg. q.i.d.	3 wk.	Good
8. S.C.	F	2 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	2 mo.	Good
9. R.F.	F	3 mo.	0	***	None	P.C.	Evap. milk	5 mg. q.i.d.	2 wk.	Good
10. A.G.	M	7 wk.	***	0	None	P.C.	Evap. milk	5 mg. q.i.d.	3 wk.	Good
11. R.I.	M	2 mo.	0	**	None	P.C.	Evap. milk	5 mg. q.i.d. and q.4 h.	1 mo.	Poor
12. P.M.	M	2 mo.	***	**	Atropine Phenobarbital	Day and night	Similac	5 mg. t.i.d.	6 wk.	Good
13. B.R.	M	1 mo.	***	0	Mesopin Phenobarbital	Day and night	Similac	5 mg. q.i.d.	1 mo.	Good
14. P.S.	F	3 wk.	***	**	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Good
15. M.S.	M	1 mo.	0	***	None	P.C.	Breast	5 mg. q.4 h.	1 mo.	Good
16. J.S.	F	1½ wk.	***	0	None	Day and night	Evap. milk	5 mg. t.i.d.	3 wk.	Good
17. E.S.	M	2 mo.	0	**	Mesopin Phenobarbital	P.C.	Evap. milk	5 mg. t.i.d.	2 wk.	Good
18. M.S.	M	2½ mo.	0	**	None	P.C.	Similac	5 mg. t.i.d.	6 wk.	Good
19. B.S.	F	2 mo.	0	**	None	P.C.	Evap. milk	5 mg. t.i.d.	6 wk.	Mod. Good
20. S.S.	F	1 mo.	***	***	None	Day and night	Evap. milk	5 mg. q.i.d.	7 wk.	Good
21. S.S.	M	2½ mo.	***	**	None	Day and night	Whole milk	5-10 mg. t.i.d.	10 wk.	Good
22. C.S.	F	7 mo.	0	**	Atropine	P.C.	Whole milk	5 mg. t.i.d.—q.i.d.	3 wk.	Good
23. I.S.	M	3 wk.	***	**	None	Day and night	Nutramigen	5 mg. q.i.d.	2 wk.	Poor

24. B.S.	M	2 mo.	**	***	None	P.C.	Evap. milk	5 mg. t.i.d.	2 wk.	Poor
25. L.T.	F	1 mo.	***	0	None	Night	Evap. milk	5 mg. q.i.d. & q.4 h.	1 mo.	Good
26. G.S.	M	2 mo.	***	**	Atropine Phenobarbital	Day and night	Evap. milk	5 mg. q.i.d.	3 wk.	Poor
27. H.S.	M	2½ mo.	***	*	None	Night	Evap. milk	5 mg. q.i.d.		Good
28. W.S.	F	6 wk.	***	0	None	Day and night	Evap. milk and skimmed	5 mg. q.i.d.	2 wk.	Good
29. M.B.	F	1 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 wk.	Poor
30. R.A.	F	5 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 wk.	Poor
31. K.G.	M	6 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	3 wk.	Good
32. D.C.	M	3 wk.	0	***	None	P.C.	Evap. milk	5 mg. q.i.d.	2 mo.	Good
33. T.K.	F	6 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Good
34. G.L.	F	7 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Good
35. S.R.	M	1 mo.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 wk.	Poor
36. S.L.	M	1 mo.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 wk.	Poor
37. J.R.	F	2 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Good
38. J.S.	F	2 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Mod. Good
39. G.M.	F	2 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 wk.	Poor
40. S.G.	F	6 wk.	***	0	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Mod. Good
41. A.F.	F	2 wk.	***	***	None	P.C.	Evap. milk	5 mg. q.i.d.	1 mo.	Good
42. S.J.	M	7 wk.	***	0	None	Night	Goat's milk	5 mg. q.i.d.	1 mo.	Good
43. A.D.	F	5 wk.	***	***	None	Day and night	Similac	5 mg. q.4 h.	2 mo.	Good
44. D.M.	M	5 wk.	***	0	None	Night	Bremil	5 mg. q.i.d.	1 mo.	Good
45. J.M.	M	2 mo.	***	***	None	Day and night	Bremil	5 mg. q.i.d.	1 mo.	Mod. Good
46. S.G.	M	5 wk.	***	0	None	Night	Evap. milk	5 mg. t.i.d.	1 mo.	Good
47. G.	F	2 wk.	***	*	None	Day and night	Evap. milk	5 mg. q.4 h.	1 mo.	Good
48. P.S.	F	1 mo.	***	0	None	Night	Similac	5 mg. t.i.d.	1 mo.	Mod. Good
49. A.D.	F	3 wk.	***	0	None	Night	Evap. milk	5 mg. t.i.d.	6 wk.	Good
50. L.S.	M	1 wk.	***	**	None	Day and night	Evap. milk	5 mg. q.i.d.	1 mo.	Good

three developed mydriasis but no inflammatory reactions occurred. However, both skin and conjunctival tests were not of value in determining generalized sensitivity to Banthine. According to these authors, children tolerate Banthine well. No blood, renal, or liver disturbances occurred with its use. Banthine dosage for children must be individualized for each patient. A suggested approximate dosage schedule is 12.5 mg. b.i.d. or t.i.d. for newborn infants; 12.5 mg. to 25 mg. q.i.d. for infants from 1 to 12 months of age; and 12.5 mg. to 50 mg. q.i.d. for children over 1 year of age.

In our investigation no toxic effects were observed with an individual dose of 5 mg. Two infants had marked flushing with individual 10 mg. doses but did not have flushing with 5 mg. doses. Five infants received total daily doses of 30 mg. without any apparent toxic manifestations.

TABLE II. RESULTS IN FIFTY CASES OF COLIC AND VOMITING TREATED WITH BANTHINE

	GOOD	MOD. GOOD	POOR	TOTAL CASES
Colic	14	3	6	23
Vomiting	10	1	1	12
Colic and vomiting	10	2	3	15
Total	34 (68%)	6 (12%)	10 (20%)	50

RESULTS

The results in individual cases were classified as good, moderately good, or poor. Table II tabulates the results in the three categories. Over-all, there were thirty-four good results, six moderately good results, and ten poor results. Usually a good result occurred within twenty-four to forty-eight hours and was most dramatic in the cases of vomiting, and colic and vomiting. Of the eight patients who had previous drug therapy without satisfactory results, seven had good results and one had a poor result with Banthine therapy. Although definite conclusions are not justified in a series of fifty cases, we believe that Banthine bromide has a definite place in the drug therapeutic approach to infantile colic and vomiting as a symptomatic or possible curative agent. Further investigations are in progress to explore the usefulness of Banthine in pediatric therapy, particularly in x-ray proved cases of pylorospasm.

SUMMARY

1. Banthine bromide, a new anticholinergic drug, was administered to fifty infants with colic, vomiting, or both.

2. Previously reported toxic effects in adults were not observed in the infants.

3. The results were as follows: thirty-four (68 per cent) good; six (12 per cent) moderately good; and ten (20 per cent) poor.

4. Therapy with Banthine was particularly successful in the cases of vomiting or colic accompanied by vomiting.

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TREATMENT OF CONSTIPATION IN INFANCY AND CHILDHOOD

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THE problem of constipation in infancy and childhood frequently confronts the pediatrician. It has been pointed out that at times irreversible and irreparable damage is done by mothers who practice "home medication" with cathartics, laxatives, soap sticks, strong enema solutions, and the habitual use of suppositories.[1-7] Poor habit formation and an irritable bowel syndrome often result from such injudicious practices. In addition, undesirable emotional factors complicate the entire picture, and the problem must be met with understanding and sympathy on the part of the pediatrician.

Dietary measures are not always successful, particularly when emotional factors are firmly entrenched. The mother watches the stools and the child becomes conscious of the tension and reacts with deliberate retention or involuntary spasticity. The mother becomes more concerned and more tense and a vicious circle begins to operate. It is important, therefore, to use a relatively quick, safe adjunct to relieve the child, while attempting to deal psychotherapeutically with the mother.

Methyl cellulose* has been tested and found to be helpful as an adjunct in the treatment of constipation and the irritable bowel syndrome in adults.[8-11] In the present study it was similarly utilized in infants and children.

Methyl cellulose is an odorless and tasteless substance, prepared in tablets or granules, which passes through the upper part of the digestive tract in a liquid state and forms bulk only when it reaches the lower part of the ileum and colon. It does not interfere with normal digestion or absorption of food, and is nonirritating.

CLINICAL MATERIAL

Clinical material for the study consisted of infants and children in the pediatric age range, most of them without organic disease, although some children with orthopedic problems were included.*

Table I depicts the number of patients treated, classified according to age groups.

TABLE I

AGE RANGE	NO. OF PATIENTS
1-3 mo.	27
3-6 mo.	16
6-12 mo.	19
12-24 mo.	18
2-5 yr.	19
5-10 yr.	10
10 plus	6
	115

In the younger groups the granulated form of methyl cellulose was more acceptable, given in the formula or sprinkled on food. Dosages ranged between ¼ and ½ tsp. administered

Address: 39 A Gramercy Park.

*The product used in this study was supplied by Chilcott Laboratories, Division of Maltine Company, Morris Plains, N. J., in granules and 0.5 Gm. tablets, under the trade name of "Cellothyl."

*Material was drawn from the New York Foundling Hospital, the pediatric division of St. Vincent's Hospital, New York City, Rehabilitation Hospital in West Haverstraw, N. Y., and private practice.

twice or three times daily. The higher dosages at times proved more effective, even with small infants. (When put in the bottle, it was found that the mixture tends to clog the nipple holes, unless they are made especially large.) Older children took 1 or 2 tablets, three times daily. In no case was there refusal on the part of the child, as the substance is odorless and tasteless.

In a few instances constipation was acute and had not been treated previously; however, in the majority of cases dietary measures (prune juice, applesauce, increased sugar in formula, etc.) had been employed without lasting success, as had suppositories, enemas, and cathartics. This was especially true in the older age groups.

RESULTS

Out of a total of 115 patients treated, the response was excellent or good in eighty-three cases, fair in nineteen, and poor in thirteen. In other words, satisfactory results were obtained in 88.7 per cent of cases of varying severity, as depicted in Table II.

TABLE II

RESULTS WITH METHYL CELLULOSE	NO. CASES	PER CENT
Excellent or good	83	72.2
Fair	19	16.5
Poor	13	11.3

In some of the failures there were extenuating circumstances which may have been partly or wholly responsible: for example, in four of these cases constipation was neurological in origin; in one there was an anal fissure and a tight anal sphincter; in another the infant was on iron therapy and constipation was not relieved until the iron was discontinued.

On the other hand, there were several outstanding successes:

K. S., 6 years of age, with a diagnosis of spina bifida and constipation of neurological etiology, and no control of the sphincter, generally went two days without stools and had to have soap enemas for relief. After administration of methyl cellulose she managed at least one good stool daily.

C. S., 6 years of age, with a diagnosis of spina bifida and spastic paralysis, would go for three days without stools unless helped, prior to administration of methyl cellulose. Mineral oil, milk of magnesia, prune juice, and enemas were all unsuccessful in producing lasting improvement. With methyl cellulose this child had good soft stools regularly.

L. S., 12 years of age, with a diagnosis of poliomyelitis involving both lower extremities and some muscle groups in the lower abdomen, would go for three days without stools, and mineral oil, milk of magnesia, prune juice and enemas had been tried without lasting results. This child had very hard stools with one impaction, and was actually afraid of the process of emptying her bowels. Methyl cellulose was used with good results.

M. S., a normal 13-month-old child, suffering from intermittent diarrhea and constipation, responded with stools of better consistency when methyl cellulose was administered for either constipation or diarrhea.

These cases represent extremes and have been selected as illustrations because they were most difficult to handle prior to the administration of methyl cellulose. However, the majority of patients in the study were well babies who merely suffered from isolated or recurrent bouts of constipation and reacted with more frequent stools of better consistency to treatment with methyl cellulose, even after other methods had failed.

DISCUSSION

Several interesting observations were made in this series of cases. The most obvious difficulty was encountered with infants who were well established on solids, and had cut their intake of milk while refusing water. Since one of the requirements for efficient results with methyl cellulose is a high fluid intake, the inability to force adequate amounts of fluid into a resistant infant or small child was in some instances a genuine obstacle to successful treatment. Bottle-fed infants at times also completely rejected plain water, giving rise to the same problem.

For acute constipation, often one or two days of administration of methyl cellulose produced the desired results; however, short trials without result could not be considered failures in chronic cases, since at least one to two weeks of medication were frequently required before regular normal evacuations took place.

In infants and children, frequent short bouts of constipation are more common than the prolonged periods of chronic constipation encountered in adults. Methyl cellulose was particularly effective for treatment of these intermittent irregularities, especially when an emotional factor was involved. Normal bowel function could thus be restored to the child without setting up a cathartic or enema cycle, with its resulting damage to the normal habit system. While treatment was continued, the underlying factors in causation of the spasticity could be made clear to the mother, and an effort could be made toward retraining the child.

SUMMARY

Methyl cellulose (Cellothyl) was administered to 115 infants and children for acute or chronic constipation. Response was excellent or good in eighty-three cases, fair in nineteen, and poor in thirteen. This treatment was effective even when response to other methods (dietary changes, enemas, suppositories, cathartics) was poor. It was found to be particularly useful in cases of spasticity, when emotional factors between mother and child were a prominent feature.

Unless high fluid intake could be maintained, methyl cellulose treatment was at times unsuccessful. There was no rejection of methyl cellulose on the part of patients participating in this study.

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FUNCTIONAL INTESTINAL OBSTRUCTION IN THE PREMATURE NEWBORN INFANT

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INTESTINAL obstruction in the newborn infant is usually secondary to some congenital anomaly. However, on rare occasions the signs and symptoms of obstruction develop in an anatomically patent gastrointestinal tract.[1] Most commonly, obstruction under these circumstances is due to meconium ileus and the prognosis is very poor.[2] But intestinal obstruction on a purely functional basis does occur in the presence of a normal gastrointestinal tract.[3, 4] Our experience with such a case is the basis of this report.

CASE REPORT

M. D., a premature newborn infant, was delivered on April 7, 1951, in City Hospital, Cleveland, under spinal anesthesia with low forceps. The mother was a 24-year-old Negro, gravida iv, para iii, with a negative serology and Rh-positive blood. The pregnancy terminated at approximately 34 weeks, and delivery was uncomplicated. At birth, the infant appeared to be normal and weighed 2,013 grams. He received routine premature care. On the second hospital day the baby appeared slightly sluggish, but otherwise normal. On the third hospital day, feedings were started.

The infant had no bowel movements on the first day of life, but passed a normal meconium stool on the second day. Thereafter, he passed stools daily, including three transitional stools on the fifth day and two yellow stools on the sixth day.

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On the seventh hospital day, the patient's weight was 1,800 grams and he was eating well, but no bowel movement was noted. On the eighth hospital day the cord sloughed, leaving a granulating area which was questionably infected, and treatment with aqueous procaine penicillin was started. Two yellow stools were noted on this day.

On the ninth hospital day the infant appeared lethargic and regurgitated large amounts of his formula. Five yellow and one blood-streaked stools were passed. Regurgitation continued after each feeding on the tenth hospital day. Streptomycin was started because infection was suspected. By the eleventh hospital day, the patient had become quite lethargic. Regurgitation after each feeding continued and the vomitus consisted of foul-smelling brown material. A hard yellow stool was passed.

Physical examination revealed a dehydrated premature infant with moderate abdominal distention. Palpation of the abdomen revealed a hard mass 2 x 2 cm. in size in the right lower quadrant and some elongated firm masses in the upper abdomen. A scout film of the abdomen revealed several distended loops of small intestine (Fig. 1). Intravenous and subcutaneous fluids were given and oral feedings discontinued. The following day small Karo water feedings were started but the infant again began to vomit. Because of the scanty stools during the preceding several days, small enemas were given without effect. Digital examination revealed no stool in the rectum. A second scout film of the abdomen confirmed the previously noted distention. The weight of the

infant was 1,535 grams at that time. The hemogram and urinalysis were not remarkable. A diagnosis of intestinal obstruction probably due to fecal concretions was made, and operation was elected.

Fig. 1.—Scout radiographs of the abdomen taken on the ninth and tenth days of life, showing distended loops of the small bowel.

Operative Note.—Under drop ether anesthesia the peritoneal cavity was entered through a transverse incision below the navel. Marked distention of the small bowel was noted and the entire colon was found filled with a stony hard cast. This material could not be "milked" along the colon. For this reason, separate incisions, each 3 cm. long, were made in the ascending colon, transverse colon, and sigmoid, and through these openings the entire colon emptied of the hard fecal concretions. Each incision was then closed transversely and the abdomen repaired in layers. The material removed from the colon was found to be hard, inspissated stool.

Postoperatively, antibioties were continued and vitamin K was given. Gastric suction was applied via a small Levin tube, but this was discontinued within twenty-four hours. By the third week postoperatively, after a

rather stormy convalescence, the infant was able to maintain himself on oral feeding. Several small transfusions were given during this period. Ten weeks after operation, he failed to have a bowel movement for a period of seven days, but did not develop significant abdominal distention or vomiting. This situation was slowly relieved with repeated enemas. Examination (Fig. 2) and a study of the gastrointestinal tract with barium five months postoperatively revealed no abnormalities. The colon emptied normally. The stools appeared normal and tests on x-ray film showed normal tryptic activity.

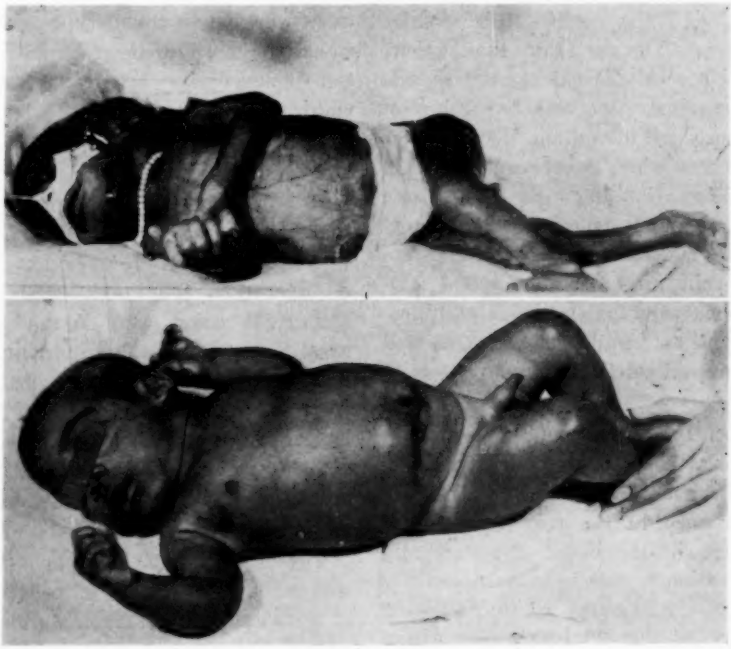

Fig. 2.—Photographs made at the age of 3 weeks and at 5 months revealing normal physical development of the patient.

DISCUSSION

This patient presented a difficult problem in diagnosis and management. Although most premature infants vomit in the first few days of life because of immaturity of reflexes and poor muscular coordination,[5] in our patient, the onset of persistent vomiting and obstipation after normal feeding and elimination suggested intestinal obstruction. Normal bowel movements during the first eight days of life seemed to eliminate the possibility of a congenital intrinsic lesion; e.g., atresia, stenosis. Gross states one-half of the cases of intestinal or colonic stenosis and all the cases of atresia have symptoms on the first day of life.[6]

Intussusception was considered as a possibility after palpation of a mass in the right lower quadrant, but failure to pass bloody mucus by rectum, the lumpiness of the abdominal mass, and the rarity of this condition in infants

under one month of age seemed to make this diagnosis unlikely.

Meconium ileus was eliminated from consideration by the infant's course. This condition results from the failure of extrinsic pancreatic secretion (pancreatic achylia) to act on the sticky meconium present in the intestine. As a result, meconium becomes inspissated and causes obstruction in the low ileum, and the condition is usually fatal.[2, 7, 8] The fact that this patient passed several normal stools was evidence against the obstruction being on the basis of meconium ileus. Other conditions which were considered in the differential diagnosis in this case were pyloric stenosis, strangulated hernia, omental cyst, abdominal abscess, congenital fibrinous bands, malrotation, volvulus, intestinal duplication, and an annular pancreas, as well as cerebral birth injury.[9, 10, 11, 12, 13, 14, 15]

Recently, Zuelzer and Wilson have described cases of intestinal obstruction, which were apparently due to a disturbance in the propulsive motor function of the bowel due to faulty innervation.[3] These authors, on the basis of eleven cases, list the following features of this syndrome. The symptoms of vomiting, abdominal distention, and the signs of intestinal obstruction usually begin at birth or shortly thereafter. The vomiting is usually of the so-called overflow type. Constipation is the rule, but several patients passed one to two small meconium stools. Digital examination reveals the presence of hard, inspissated fecal masses in the rectum and, in general, the stool is dry, hard, dark brown, and formed into pellets. The age group in this series ranged from newborn to 4 months with complete obstruction developing at birth in five cases. Five of the patients were siblings. Two of their patients survived operation and were alive with colostomies. These authors searched for evidence of ganglion cells in the myenteric plexus of the lower bowel in their material and in most instances none was found. On this basis they concluded that the obstruction in these cases was functional in type and represented the acute form of the situation which exists chronically in older children as megacolon.

Forshall, Rickham, and Mossman[4] have described a similar case of an infant who passed meconium twenty-four hours after birth but who became obstructed within forty-eight hours. At operation, the lower small bowel and right colon were found to be greatly distended. This patient died five weeks postoperatively, probably from recurrent obstruction. Histological studies revealed scanty myenteric and submucosal ganglia in the cecum and none beyond the transverse colon.

The decision to operate in our case was made on the basis of progression of signs and symptoms compatible with mechanical intestinal obstruction. Once the peritoneal cavity was entered it appeared that the preoperative diagnosis was correct. The entire colon from cecum to rectum was filled with a stony hard cast which resisted all attempts to "milk" it along into the rectum for manual extraction. This seemed at once to exclude meconium ileus as the cause of the obstruction since in this condition the obstructing meconium is usually lodged in the lower ileum, rarely in the right colon but never beyond this point.

Ileostomy, although capable of relieving this type of obstruction, was not done because of the severe postoperative fluid and nutritional problems which were anticipated with this type of procedure in a 1,500 gram infant. Multiple colotomies were done instead of a cecostomy or colostomy because it was felt that the infant's best chance for survival was in the presence of a functionally intact bowel. This was done with awareness of the possibility that a second operation might be necessary if the condition recurred. However, except for the episode ten weeks after operation, no further return of obstipation has been noted.

Certainly, our case resembles the syndrome described by Zuelzer and Wilson. However, the entire process in our patient might well have been due simply to a hypotonic bowel, a situation which prevails not infrequently in premature infants and causes constipation.[5] In these infants there is very little reaction of the mucous membrane of the bowel to mechanical and chemical stimulation and the muscle wall contains very little power. This produces stasis, abnormal reabsorption of fluid from the stool, and consequent fecal impaction. Only prolonged observation will enable us to determine whether megacolon will develop in this child.

SUMMARY

1. A case of functional obstruction with fecal impaction in a premature infant and a differential diagnosis has been presented briefly.

2. The patient was operated upon and the fecal concretions evacuated through multiple colotomies. Following primary closure and a stormy convalescence, the patient has done well.

3. The similarity between this patient and others reported with absent ganglion cells in the myenteric plexus of the lower bowel is discussed.

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REDUCTION OF MORTALITY IN THE PREMATURE NURSERY

I. The Declining Role of Infection as a Major Cause of Mortality in the Modern Premature Nursery

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IT is an accepted conclusion that the premature infant is highly susceptible to infection and that infection constitutes a major hazard in the premature nursery.[1] In the well-conducted premature nursery, protecting the infant from this hazard is a cardinal principle.[2, 3, 4] Reardon and associates,[3] in a recent review of premature care, reported that most premature infants' deaths are due to infection.

In the constant effort to increase the survival rate of the premature newborn infants in our nursery, we undertook the following investigations:

1. To evaluate the role of postnatal infection on the mortality rate in a modern premature nursery.
2. To determine whether penicillin given prophylactically to premature newborn infants can influence the incidence of postnatal infection and the fatality rate.

PROCEDURE

These studies were done in the premature nursery of the Beth-El Hospital where every technique for the prevention of postnatal infection is strictly adhered to. On admission to the premature nursery, each newborn infant was given intramuscularly 150,000 units procaine penicillin G in aqueous suspension. This dose of penicillin was repeated for five consecutive days. In the fatal cases, the number of injections administered was limited by the period of survival.

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OBSERVATIONS

Our observations are presented in four tables.

Table I indicates the important data concerning our patients. Penicillin was administered to 180 newborn infants. There were twenty-eight deaths, giving a mortality rate of 15.5 per cent for infants under 2,270 grams (5 pounds) at birth. There was a great loss of infants in birth weight groups 1 and 2. Twenty-five per cent of the premature infants had a birth weight of less than 1,500 grams, but contributed 75 per cent of the mortality.

Table II notes the survival period for the fatal cases. Fifty-seven per cent survived less than twenty-four hours, 75 per cent less than forty-eight hours, 96 per cent survived less than one week. Twenty-seven of the twenty-eight deaths took place in the first week of life.

Table III shows the pathological findings in the twenty-eight fatal cases. Atelectasis was found in

TABLE I. SUMMARY OF CASES

BIRTH WEIGHT GROUPS	NUMBER OF INFANTS	BIRTH WEIGHT (GRAMS)	NUMBER OF DEATHS	PER CENT MORTALITY
1	15	1,000 or less	14	93
2	29	1,001-1,500	7	25
3	59	1,501-2,000	4	7
4	77	2,001-2,270	3	4
Total	180		28	15.5

TABLE II. PERIOD OF SURVIVAL FOR FATAL CASES

	LESS THAN 24 HOURS	24-48 HOURS	2-7 DAYS	7-30 DAYS	TOTAL
Number of infants	16	5	6	1	28
Per cent	57	18	21	4	100

twenty-two cases, petechial hemorrhages in various organs in twelve, hyaline membranes in the alveolar spaces in nine, liver degeneration in seven, bronchopneumonia in five, aspiration of vernix in five, intraventricular hemorrhage in two, congenital anomalies in three, focal adrenal necrosis in two.

TABLE III. PATHOLOGICAL FINDINGS IN FATAL CASES

	BIRTH WEIGHT GROUP				
	1	2	3	4	TOTAL
Number of fatal cases	14	7	4	3	28
Atelectasis	13	5	2	2	22
Intraventricular hemorrhage	1		1		2
Congenital anomaly		1	1	1	3
Hyaline membrane of lung	2	4	1	2	9
Bronchopneumonia	3	1		1	5
Petechial hemorrhages	5	2	2	3	12
Focal adrenal necrosis	1			1	2
Liver degeneration	2	1	1	3	7
Aspiration of vernix	3		1	1	5

In Table IV, the detailed pathological observations in the five cases of bronchopneumonia are presented. Two patients survived less than twenty-four hours. One survived eleven days with a fatal anomaly. One survived four days with atelectasis and petechial hemorrhages. One survived two days with atelectasis and petechial hemorrhages.

Pulmonary hyaline membrane was found in nine infants who died within the first forty-eight hours after delivery. The earliest death occurred at eight hours. This corresponds to the recent observations of Blystad, Landing, and Smith[7] that respirations for at least one hour are essential for hyaline membrane formation.

TABLE IV. PATHOLOGICAL FINDINGS IN CASES WITH BRONCHOPNEUMONIA

	BIRTH WEIGHT GROUP		
	1	2	4
Number of fatal cases	14	7	3
Bronchopneumonia	3	1	1
Period of survival	4 da. 2 da. 17 hr.	11 da.	22 hr.
Atelectasis	3		1
Petechial hemorrhages	3	1	
Hyaline membrane of lung			1
Liver degeneration			1
Congenital anomaly		1	
Aspiration of vernix	1		

OBSERVATIONS ON THROAT CULTURES

Throat cultures were taken from sixteen infants before and after a penicillin series. Our purpose was to ascertain whether any changes occurred in the bacterial flora. The following observations were made:

1. Sterilization of the throat was not noted in any of the infants after a penicillin series.
2. In three patients, the flora was altered. A growth of *B. coli* appeared in one infant; and a growth of Friedländer's bacillus in the other two.

From this small series, it appears that penicillin may be inadequate and perhaps dangerous when used alone in the treatment or prevention of infection in the premature infant. Since penicillin attacks most gram-positive bacteria, it is conceivable that the removal of this group may increase the pathogenic activity of gram-negative bacteria, particularly *B. coli*, to which the newborn and the infant are definitely susceptible.

DISCUSSION

The incidence of postnatal infection, in our series, was small. This fact could not be attributed to the effects of penicillin prophylaxis. Yet, there was only one death, of the twenty-eight total, that occurred after the seventh day of life, or after the time the penicillin prophylactic treatment could be considered effective. Hence, it might be considered, since we had no deaths after the seventh day, that this proved the effectiveness of penicillin. However, comparison with our previous experiences without penicillin in 992 premature infants showed that we had not altered the hospital's mortality rate for premature infants, the survival period for fatal cases, and the percentage mortality in each weight group.[5]

In our cases, as was also evident from other reports,[1, 4, 5, 8] fatalities originated principally in the lower weight groups. We obtained, consequently, a clearer insight to our premature infant mortality by examination of the birth weight groups, the percentage mortality for each weight group and the period of survival of the fatal cases. It was evident that, rather than infection, the serious obstacles to the reduction of mortality in the modern premature nursery are the following:

1. The great loss of premature lives in the lower weight groups. (In contrast, an insignificant loss in the upper weight classification.)
2. The short survival period of less than twenty-four hours in 60 per cent and less than one week in 95 per cent of fatal cases. (This situation permits only a limited time for application of supportive measures.)
3. The inadequacy of available means to successfully sustain life and speed up the process of growth and development of most premature infants born in the fatal low weight group to a level essential for life.

Other investigators have likewise recognized the reality of this approach to premature mortality.

Tyson[10] stated: "There is no question of doubt that the birth weight of premature infants is an important factor in their survival."

Miller[11] reached a similar conclusion: "The mortality among live-born premature infants is determined almost wholly by their birth weight."

Dunham,[1] in an analysis of the period of survival for fatal cases (based on data from the U. S. Bureau of the Census), reported: "Almost all (97 per cent) of the deaths attributed to premature birth in 1944 occurred in the first month of life. The first day was the most critical period with 57 per cent of the deaths; 29 per cent occurred from the second to the seventh day; and 10 per cent from the second week to the first month."

Moncrieff[4] observed the high mortality in premature infants born in the lower weight groups and concluded: "The program of management must be designed to speed up the process of maturation."

Reardon's conclusion,[3] that the incidence of infection and the loss of premature lives from infection contributed predominantly to premature mortality, was definitely not valid in our nursery. In the well-conducted premature nursery, postnatal infection is only a minor factor in mortality.[5, 6, 8, 9]

A premature nursery conducted as advised by the American Academy of Pediatrics[2] is, at present, the surest method of safeguarding infants from postnatal infection.

CONCLUSIONS

1. In the modern premature nursery, the influence of postnatal infection on the fatality rate is insignificant.

2. A premature nursery conducted as advised by the American Academy of Pediatrics is the surest method of safeguarding infants from postnatal infection.

3. There is a great loss of premature lives in the lower weight groups and an insignificant loss in the upper weight groups.

4. More than 95 per cent of all fatal cases in the premature nursery have a survival time of less than one week.

5. Further reduction in mortality can be attained by:

a. Research in the cause and prevention of prematurity.

b. Research designed to sustain life and accelerate the processes of growth and development of the premature infants born in the lower weight groups to a level essential for life.

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GANGRENE OF THE EXTREMITIES IN THE NEWBORN INFANT

Report of Two Cases

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MOST physicians have never seen gangrene occur in the newborn infant. Only one of twelve prominent obstetricians questioned by Steiner had any personal knowledge of this condition.[1]

A review of the literature by Heller and Alvari in 1941 summarized forty cases going back to 1828, and included thirty-five reports from foreign periodicals.[2] Ten more have been added by Gross,[3] Steiner,[1] Leveuf, Laurence, and Mallet,[4] Israels and Stein,[5] Perlmutter and Wagner.[6] Including the two patients to be described, there are fifty-two on record.

Twice as many babies were afflicted in the lower extremities as in the upper limbs. Death occurred in seventeen cases, recovery with gross mutilation in seventeen, and functional recovery in thirteen (see Table I).

CASE REPORTS

The present report describes an infant treated with vasodilating agents and heparin, and an infant delivered by cesarean section in whom gangrene of an extremity was noted at birth.†

Case 1.—W. K., a white, male infant, was born Jan. 10, 1950, at the Norwegian Hospital, after an uneventful forty-week gestation. The mother was 25 years old, gravida iii, para ii. Two children were healthy. Her prenatal Wassermann was negative. During the two hours and forty-seven minutes of labor she received 100 mg. of Demerol. In the delivery room the only anesthetic was nitrous oxide and oxygen. The infant was born without difficulty in a footling, left sacral anterior position. He cried and breathed spontaneously. Birth weight was 4.25 kilograms (9 pounds, 6 ounces), and total length was 54 centimeters.

During the second stage of labor the left arm was at the baby's side and, at

Table I. Anatomical Distribution of Gangrene and Results (Fifty-Two Cases)

	Heller, Alvari	Leveuf, Laurence, Mallet	Steiner	Israels, Stein	Perlmutter Wagner	Gross	Askue, Wong	Total
Extremity affected								
1. Upper	9	2	1	0	0	1	2	15
A. Right	6	0	0	0	0	1	0	7
B. Left	3	2	1	0	0	0	2	8
C. Both	4	0	0	0	0	0	0	4
2. Lower	24	0	1	1	1	3	0	30
3. Scattered	7	0	0	0	0	0	0	7
Result								
1. Death	16	0	0	0	0	1	0	17
2. Recovery with gross mutilation	9	2	1	1	0	2	2	17
3. Functional recovery	10	0	1	0	1	1	0	13
4. In doubt	5	0	0	0	0	0	0	5

Both cases reported by courtesy of Dr. John A. Monfort.

This paper was read in part before the Brooklyn Academy of Pediatrics, April 26, 1950.

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†In a case previously reported by Gross, signs of arterial occlusion were noted several hours after delivery by cesarean section.[3]

first, appeared normal. About twenty minutes after birth, the hand and distal two-thirds of the forearm became white. Within a few hours this area was purple, the nails deeply cyanotic, and the discolored parts cold. The infant did not move the left arm as readily as the right. There were no other physical abnormalities. The attendants' first impression was that the cause was either a fracture of the upper extremity or an injury to the brachial plexus.

Roentgenograms showed no fracture or other defect of the affected extremity. Red blood cell count was 5.26 million, hemoglobin 23 grams, white blood count 16,050 with 66 per cent polymorphonuclears, 33 per cent lymphocytes, 1 per cent monocytes. Urinalysis was unremarkable. Blood sugar (micromethod, not fasting) was 160 mg. per 100 c.c. of blood.

By January 12, the third day of life, there was a sharp line of demarcation between healthy and diseased tissue. The lower two-thirds of the forearm were purple-white, the hand purple, and the finger tips black. On elevation the hand became paler. There was no edema. (See Fig. 1.) Peripheral pulses were not palpable. On this date vigorous treatment was begun to encourage collateral circulation and to prevent thrombus formation which is often associated with arterial occlusion.[7] Immediately after 2 mg. of papaverine hydrochloride were given intravenously, a slight pink flush appeared at the base of the second and third digits. The following schedule was initiated: 2 mg. papaverine intramuscularly every four hours, 50,000 units of penicillin intramuscularly every three hours, 25 mg. Priscoline hydrochloride (2-benzyl-imidazoline hydrochloride) orally every four hours, 10 drops of whiskey in each of the six daily feedings. The hand and forearm were wrapped in sterile cotton, kept below the level of the body and disturbed as little as possible. Feedings consisted of pumped breast milk. A water-soluble multiple-vitamin preparation was given daily.

Heparin was chosen as the anticoagulant instead of Dicumarol in order to avoid the frequent venipunctures required to follow the prothrombin time when the latter compound is used. For the same reason clotting times were measured by the capillary tube method instead of the more accurate Lee-White method. Clotting times were determined every twelve hours and the daily dose of Depo-Heparin Sodium given subcutaneously after the morning measurement. Because of uncertainty concerning the heparin tolerance of the newborn infant, the first dose of Depo-Heparin was 8 mg. or about half the

Fig. 1 (Case 1).—Early gangrene on the third day of life.

dose calculated in proportion to body weight. The dose of repository heparin was increased daily until the desired effect on the clotting time was obtained following the administration of 75 to 100 mg. (see Table II and Fig. 2). On January 19, twelve hours after 100 mg. of Depo-Heparin had been given, the baby vomited a small amount of bright red blood. At that time the clotting time was 20 minutes. The following day there was serosanguineous oozing from the base of the separating umbilical cord and bleeding from the site of a penicillin injection.

The heparin dosage that day was 50 mg., the clotting time 9 minutes.

After each dose of Priscoline the baby's entire body flushed briefly with slight improvement in the color of the gangrenous tissue. On January 16, the fifth day of treatment, the Priscoline was increased to 37.5 mg. every four hours, and the whiskey increased to 10 drops with each feeding. Because of vomiting on the following day, the Priscoline was reduced to 25 mg. every four hours. After January 16 the hand was kept constantly elevated because of the onset of swelling. Vomiting became persistent, necessitating cessation of oral administration of Priscoline on January 23. An intramuscular form of this compound was tried, 25 mg. was injected every six hours, but was discontinued because of emesis within fifteen minutes after each injection.

TABLE II. CHANGES IN BODY WEIGHT AND RELATION OF HEPARIN DOSAGE TO CLOTTING TIMES (CASE 1)

DATE	CLOTTING TIME (MIN.)	DEPO-HEPARIN (MG.)	WEIGHT
1/13/50	4½	8	
	4½		
1/14/50	3½	16	
1/15/50	4	18	
	5		
1/16/50	4	32	8 pounds, 1 ounce (3.66 kilograms)
	8		
1/17/50	6	50	
	5		
1/18/50	5	75	
	10		
1/19/50	4	100	
	20		
1/20/50	9	50	
1/21/50	10	75	
	27		
	15		
1/22/50	8	75	
	9		
1/23/50	4½	75	7 pounds, 8½ ounces (3.42 kilograms)
	8		
1/24/50	6	100	
	60		
	29		
1/25/50	5	87½	7 pounds, 10½ ounces (3.47 kilograms)
	10		
1/26/50	5	90	
	25		
1/27/50	7	90	7 pounds, 8¾ ounces (3.43 kilograms)
	60		
1/28/50	5	90	
1/29/50	5	Discontinued	
1/30/50		Amputation	
2/2/50			8 pounds, 8 ounces (3.86 kilograms)
2/3/50			8 pounds, 14 ounces (4.03 kilograms)
2/6/50		Second operation	9 pounds, 1 ounce (4.11 kilograms)
2/8/50			9 pounds, 8 ounces (4.31 kilograms)
2/9/50			9 pounds, 9 ounces (4.34 kilograms)
2/10/50			9 pounds, 9 ounces (4.34 kilograms)
2/11/50			9 pounds, 8 ounces (4.31 kilograms)

By January 28 the area of healthy tissue had increased so that the line of demarcation moved distally to the junction of middle and distal thirds of the forearm. The fingers were rigidly flexed, the fingers and hand edematous and purple except for small

pink areas at the base of the second and third digits. There was an area of sloughing about 2.5 cm. square on the radial flexor surface of the wrist. (See

represented a 21 per cent loss from birth weight. Because of the poor fluid intake, frequent hypodermoclyses had become necessary. The eyes were

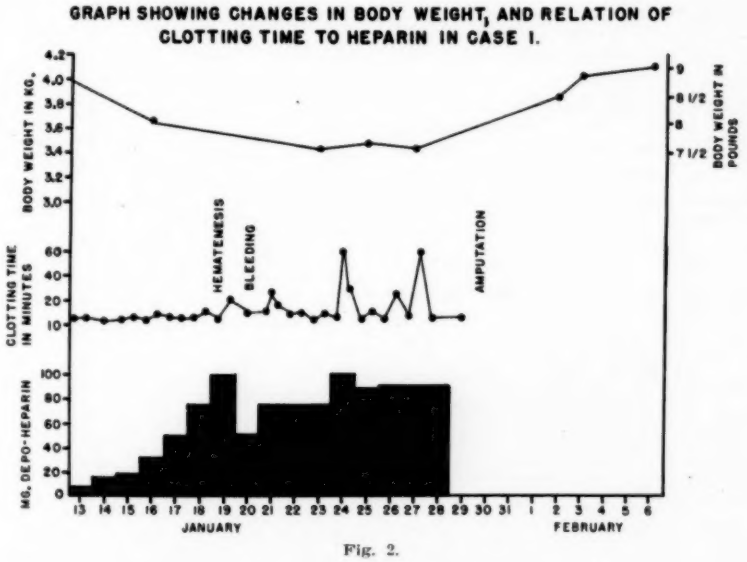

Fig. 2.

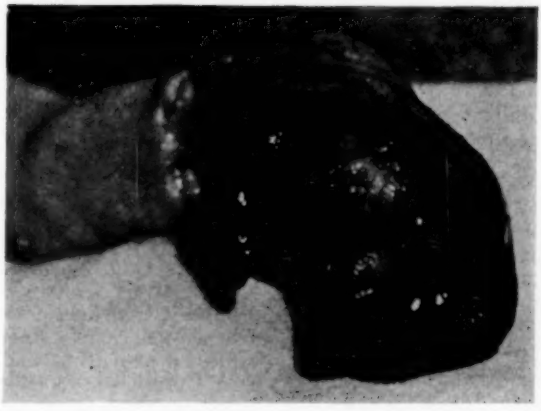

Fig. 3 (Case 1).—Advanced gangrene on the nineteenth day of life.

Fig. 3.) The necrotic tissues did not have an offensive odor.

At that time (the nineteenth day of life) the infant's weight was 3.42 kilograms (7 pounds, 8½ ounces) which

sunken, and, although there was no fever and the dead tissue did not appear grossly infected, the infant impressed observers as being toxic. The red blood cells were 5.03 million, white

blood cells 23,700, with 87 per cent polymorphonuclears, 13 per cent lymphocytes.

Papaverine and heparin were discontinued. In addition to penicillin, sulfadiazine was given 0.1 Gm. every four hours for twenty-four hours, and then 0.05 Gm. every four hours for the next ten days.

On January 30, the twenty-first day of life, the left forearm was amputated at the junction of upper and middle thirds. To prevent osteomyelitis a petrolatum gauze pack dusted with sulfadiazine was affixed to the stump with two sutures. On February 6 the gauze was removed, the wound irrigated with saline, and the skin flaps approximated with interrupted silk sutures. A moulded plaster splint immobilized the arm in extension.

Dissection of the surgical specimen showed, "Apparently normal radial and ulnar arteries up to the level of the necrotic tissue. Normal vessels could also be traced to the dorsum of the second and third digits, whereas no healthy looking vessel could be identified traversing the necrotic tissue of the palm. Grossly no points of occlusion could be established other than at the level of general necrosis." Microscopic sections of the necrotic areas revealed, "local clumps of basophilic staining cocci in areas that did not show any infiltration of inflammatory cells in the immediate vicinity."

Immediately after the first operation the infant's general condition improved. He ate well and by the time of discharge on February 18 he had regained his birth weight. The wound healed quickly and well.

He was seen several months later by his family physician, when he was in excellent health. He held his bottle with the aid of the amputation stump.

CASE 2.—F. C., a 3.66 kilogram (8 pound, 1 ounce) female infant, was delivered by cesarean section on Jan. 29, 1950, at the Swedish Hospital, Brooklyn. The operation was performed after thirty-nine weeks of gestation because of pelvic disproportion. The mother, a 23-year-old gravida i, para 0, had had an uneventful pregnancy except for urticaria two weeks ante partum treated with an unknown antihistaminic agent. There had been mild vaginal spotting for one week prior to the delivery. The mother's Wassermann test had been negative during the pregnancy. She had no labor and the membranes were intact at the time of surgical intervention. The only anesthetic was intratheeal procaine. The placenta, cord, and membranes were grossly normal.

There was no apparent defect other than that of the left upper extremity. There was a constriction band 4 cm. wide around the lower third of the forearm. Distal to this the skin was blackened with several large blebs on the dorsum of the hand. The radial pulse was absent, and there was no active motion in the wrist or hand. Treatment consisted of 30,000 units of penicillin intramuscularly every three hours, local boric acid compresses, and elevation of the extremity. On January 30, the second day of life, the constriction band was excised, and some necrotic tissue was removed from the dorsum of the hand.

For three days postoperatively the infant was listless and regurgitated part of her feedings. On February 1, her hemoglobin was 7.4 grams, red blood cells, 3.25 million, white blood cells, 11,600, with 51 per cent polymorphonuclears, 34 per cent lymphocytes, 6 per cent eosinophils. After a transfusion of 50 c.c. of whole blood on February 2, the hemoglobin rose to 9.6 grams. Transfusions of 100 and 50 c.c. were given on February 3 and 4 respectively. There was a moderate, transient urticaria following the last transfusion. On February 6 the aqueous penicillin was discontinued, and Crysticillin 300,000 units intramuscularly was given once a day thereafter during the remainder of the hospitalization. At no time was the rectal temperature more than 100° F.

By February 6 the distal third of the forearm, the hand, and fingers had become withered, hard, and dark brown. The line of demarcation be-

tween live and dead tissues was distinct. Where the constriction ring had been removed the wrist was very thin, and blackened tendons were visible. The fingers were rigidly flexed. There was no gross evidence of infection. (See Fig. 4.)

On February 7, under ether and oxygen anesthesia, a guillotine amputation was performed distal to the insertion of the biceps muscle. Muscles, fascia, and skin were approximated over the stumps of the radius and ulna with continuous sutures. A drain was placed in the stump. The postoperative course was uneventful. Sutures and drain were removed on February 13. The infant was discharged from the hospital in good condition two days later. At that time she had regained her birth weight.

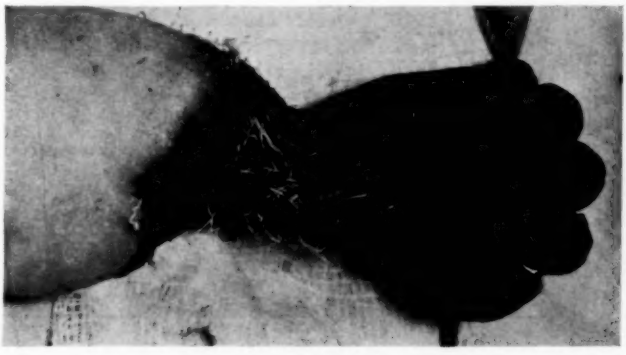

Fig. 4 (Case 2).—Advanced gangrene on the ninth day of life.

The pathologist's description of the surgical specimen stated, "The specimen consisted of a mummified left hand and forearm. There was a collar of viable tissue at the proximal extremity 0.5 cm. in width completely encircling the cut ends of the radius and ulna. The hand showed five fingers fixed in flexion, which were hard and black. Blackened tendons were seen at the wrist. The underlying muscle appeared normal. Smooth blood vessels which appeared patent could be made out. Microscopic section revealed replacement of muscle tissue by fibrous connective tissue and a moderate infiltration with inflammatory cells principally of the lymphoid and mononuclear variety. Many small and medium-sized vessels were seen whose lumens were completely obliterated by loose fibrous tissue. Diagnosis: Left forearm and hand with dry gangrene."

COMMENT

According to Allen, Barker, and Hines, arterial occlusion can result from (1) arterial spasm, (2) arterial thrombosis, and (3) emboli obstructing the arterial lumen.[7]

Through sympathetic nerve pathways arterial occlusion can initiate reflex arteriospasm in collateral vessels. This factor must be considered in the treatment of arterial occlusion to prevent irreversible intimal damage and thrombosis following vasospasm. Arteriospasm can also be produced by heavy metals, drug poisoning (ergot), neurogenic lesions, or direct trauma to the artery. Injury to an artery stimulates sympathetic reflex vasospasm.

Arterial thrombosis may be a sequel of severe blunt trauma, penetrating wounds or repeated trauma. Nontraumatic arterial thrombosis occurs in certain infectious diseases such as typhoid fever and pneumonia in which

there may be slowing of blood flow, increased blood coagulability, and intimal changes. Arterial thrombotic processes may also occur in blood dyscrasias (anemias and polycythemia), congestive heart failure, postoperative states, venous thrombosis, and in an "idiopathic" situation known as thrombophilia characterized by an elevated platelet count and an increased tendency of the blood to coagulate.

Emboli from large placental infarcts might theoretically produce arterial occlusion in the fetus although this relationship has never been demonstrated. In this connection it might be mentioned that the placenta was grossly normal in Case 2 in which arterial occlusion occurred in utero.

Though gangrene of the extremities is not seen after most difficult and traumatic deliveries, it is impossible to

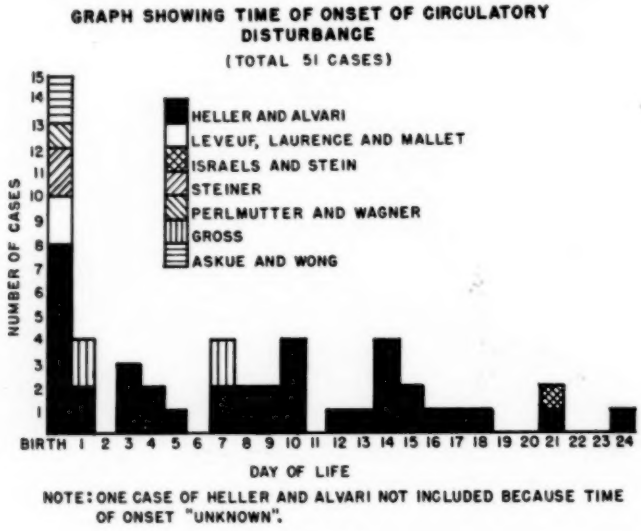
GRAPH SHOWING TIME OF ONSET OF CIRCULATORY DISTURBANCE
(TOTAL 51 CASES)
HELLER AND ALVARI
LEVEUF, LAURENCE AND MALLET
ISRAELS AND STEIN
STEINER
PERLMUTTER AND WAGNER
GROSS
ASKUE AND WONG
NUMBER OF CASES
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
BIRTH 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
DAY OF LIFE
NOTE: ONE CASE OF HELLER AND ALVARI NOT INCLUDED BECAUSE TIME OF ONSET "UNKNOWN".

Fig. 5.

Arterial emboli originate from the heart, arterial mural thrombi, aneurysms, traumatized and inflamed areas.[7]

It is of interest to relate these causes of arterial occlusion taken from Allen, Barker, and Hines[7] to actual instances observed during the neonatal period. Explanation should be sought for the relatively high incidence of cases noted at birth or shortly thereafter (Fig. 5), and for the fact that the lower extremities have been affected twice as often as the upper (Table II).

dismiss birth trauma as an etiological factor. Among the fifty-two reported cases, sixteen were described as difficult, traumatic, or "dry" labors.[1, 2, 3, 4, 5, 6] (See Table III.) Since direct trauma to arteries will produce angiospasm, arterial thrombosis, or emboli, there are a number of theoretical mechanisms to explain the possible relationship of birth trauma and arterial occlusion. Steiner described a dry labor in which the affected fingers were pressed between the fetal head and maternal pelvis.[1]

It is difficult to comprehend how the umbilical cord encircling a limb could produce gangrene without first compromising the cord circulation to an extent that would prove fatal to the baby. However, Steiner reported an instance suggestive of this mechanism. Following a prolonged dry labor, a baby was born in whom immediately proximal to a gangrenous thigh and leg was a groove into which the umbilical cord fitted.[1]

Neonatal circulatory adjustments such as thrombotic closure of the ductus arteriosus and thrombosis of the umbilical arteries are probably responsible for emboli and extensions of thrombi producing a number of instances of arterial occlusion. Both mechanisms could account for circulatory changes in the lower extremities, but only emboli from the ductus arteriosus could affect the upper. Gross described an autopsy of a baby with thrombosis of the umbilical arteries which had progressed into the hypogastric and common iliac arteries and then ascended the aorta compromising the circulation to the lower extremities.[3] Emboli might pass into the left common carotid, left subclavian, or descending aorta, but could hardly enter the innominate artery to cut off the blood supply to the right arm. If this process were important as a cause of gangrene in the upper extremity, one would expect a preponderance of instances in which the left arm was affected, a supposition not confirmed by actual experience. Reference to Table I shows seven reports of gangrene in the right upper extremity, and eight in the left. Indeed, Taussig in describing the normal anatomy of the ductus arteriosus states that it "opens into the aorta beyond the origin of the left subclavian,"[8] making it difficult to understand how emboli from this source could pass against the arterial stream to embarrass the circulation to either arm. It is not unreasonable to suppose that emboli from the ductus arteriosus could obstruct arteries in the lower extremities.

TABLE III. TYPE OF DELIVERY ASSOCIATED WITH NEONATAL GANGRENE

DESCRIPTION OF DELIVERY	HELLER, ALVARI	LEVEUF, LAURENCE, MALLET	STEINER	ISRAELS, STEIN	PERLMUTTER, WAGNER	GROSS	ASKUE, WONG	TOTAL
Difficult or traumatic	14	0	0	0	1	0	0	15
Dry labor	0	0	2	0	0	0	0	2
Normal	14	2	0	1	0	3	0	20
Cesarean section	0	0	0	0	0	1	1	2
Breech without trauma	0	0	0	0	0	0	1	1
Unknown	12	0	0	0	0	0	0	12
								52

Since polycythemia is a predisposing condition in arterial thrombosis, one might speculate concerning relationship of the newborn infant's plethora to his relative susceptibility to arterial occlusion.

Infections such as typhoid fever and pneumonia which produce intimal changes, increased coagulability of the blood, and slowing of blood flow are in no way peculiar to the newborn infant. Bacterial emboli from sepsis are not large enough to occlude major blood vessels, but only produce small areas of localized necrosis secondary to cellulitis. Congenital cardiac defects with

nonseptic vegetations from anomalous valves, compensatory polycythemia, and arrythmias are potential causes of arterial occlusion and should be considered in the individual case.

Allergic mechanisms have never been mentioned as playing a role but it is at least suggestive that the mother of the patient in Case 2 reported here had urticaria near the end of pregnancy and the infant had urticaria following a transfusion.

Earlier authors quoted in the review by Heller and Alveri mentioned "Reynaud's disease, syphilis, trauma to mother and diabetes mellitus" as etiological factors which have not seemed plausible to contemporary writers. (See Table IV.)

Signs of Arterial Occlusion.—The manifestations of arterial obstruction are sudden onset of coldness, pallor, diminution or loss of muscle strength, discoloration of the skin, and absence of arterial pulse distal to the point of obstruction.[3] The paralysis of an extremity of the neonatal period will often suggest a fracture or brachial plexus injury.

Prognosis.—Factors which determine the extent of tissue damage are the size of the obstructed artery and the efficiency of the collateral circulation. If gangrene occurs, demarcation between healthy and affected tissues appears in twenty-four to forty-eight hours. Should the process be reversible, the pale or cyanotic skin becomes pinker and the skin temperature rises. Sometimes the earliest changes characteristic of recovery do not appear for a week or more. Recovery of muscle function may not be complete for weeks or months. Residual changes from ischemia may be fibrosis and contractural deformities. Considerable and often unexpected recovery may occur after severe ischemia.[3]

Most of the deaths were reported before the use of sulfonamides and antibiotics, so one might conclude that control of infection has reduced the hazard to life. (See Table I.)

Treatment (with general measures applicable to the infant).—For best results the condition should be recognized and treated promptly. Delay may allow irreversible damage to the intima of blood vessels neighboring and

TABLE IV. CONDITIONS MENTIONED BY AUTHORS AS COEXISTENT WITH OR CAUSATIVE OF NEONATAL GANGRENE

	HELLER, ALVARI	LEVEUF, LAURENCE, MALLET	STEINER	ISRAELS, STEIN	PERLMUTTER, WAGNER	GROSS	ASKUE, WONG	TOTAL
Presumably pressure	5	0	2	0	0	0	0	7
Presumably infection	6	0	0	0	0	0	0	6
"Reynaud's or other neurological disorder"	7	0	0	0	0	0	0	7
Thrombi	4	0	0	0	0	0	0	4
Syphilis	1	0	0	0	0	0	0	1
Trauma to mother	1	0	0	0	0	0	0	1
Thrombosis of ductus arteriosus and umbilical arteries	0	0	0	0	0	1	0	1
Unknown	15	2	0	1	1	3	2	24
Diabetes mellitus	1	0	0	0	0	0	0	1
								52

distal to the occlusion, thus creating a situation favorable for thrombosis and ischemia which after a period of time cannot be overcome. Perhaps better results might have been obtained in our first case if vigorous therapy had been instituted earlier.

Objectives of treatment are (1) to minimize trauma to diseased tissues, (2) to prevent infection, (3) to discourage thrombotic processes, (4) to increase collateral blood flow, and (5) to avoid or delay amputation as long as life is not endangered.

The affected extremity should be wrapped in sterile absorbent cotton which can be changed daily. Attendants should handle the limb as little as possible, even feeding the baby (pumped breast milk or formula) without lifting him out of the bassinet. Administration of penicillin is an advisable prophylactic measure against infection.

Anticoagulants prevent growth of thrombi at the site of occlusion and inhibit thromboses in neighboring vessels predisposed to this process by reflex vasospasm.

Dicumarol can be given by mouth but its dosage must be regulated by daily measurement of prothrombin times. The onset of effect is slower than that of heparin. Heparin can be given intravenously and the resultant prolongation of coagulation time used to determine the dose of repository heparin. To date there have been no known studies on heparin tolerance in newborn infants. The only other reported instance in which heparin was administered to an infant was a 1-year-old boy who was given Depo-Heparin 50 mg. every six hours for fifty-four days as part of the treatment for thrombosis of femoral artery. Coagulation times were not reported.[9] The high dosages necessary in Case 1, which were about two to four times the anticipated requirement on the basis of body weight, should not be considered a precedent for high dosages of heparin without preliminary heparin tolerance studies in the individual infant.

Arterial blood flow should be encouraged by keeping the affected limb lower than the heart. This position may have to be modified if edema appears.

The application of external heat increases the necrosis of ischemic tissue by increasing local metabolic requirements. External heat may be applied to other parts of the body so that the ischemic limb benefits by reflex vasodilation, but *never* to the affected area. An ice pack applied to the diseased extremity may be of benefit.[3]

Gross used 5 c.c. of procaine in lumbar sympathetic nerve blocks in one instance to produce vasodilation.[3] This is a widely accepted procedure for treatment of vascular occlusion in adult medicine,[7, 10] but there is little mention of it in pediatric literature.

Other vasodilating measures are the administration of Priscoline (in doses sufficiently large to produce flushing of the skin), intravenously or intramuscularly injected papaverine, and ethyl alcohol by mouth.

In adults, if such measures are instituted later than twenty-four hours after the arterial occlusion, recovery of the limb cannot be expected in more than 50 per cent of instances.[10] Although theoretically better results might be anticipated in therapy during the neonatal period because of the more adaptable collateral arteries, reliance should not be placed on this

possibility. Vigorous therapy should be started early.

In adults, embolectomy is an accepted procedure to relieve arterial occlusion in selected instances. There is no known precedent, however, for this procedure in infants. The minute caliber of infantile arteries may be a technical consideration which has deterred surgeons from attempting the operation.

When the outcome appears unfavorable for function or survival of the extremity, the selection of time for amputation becomes an important consideration. Unless the infant's general condition deteriorates as the result of gangrene, amputatiou should be delayed as long as there is any possibility of tissue recovery. A number of instances of apparently irreversible gangrene have terminated in normal or functionally useful extremities.[3]

SUMMARY

1. Gangrene of an extremity is described in two newborn infants, increasing to fifty-two the number of reported cases. The reported instances are reviewed in respect to age of onset, location of gangrene, probable causes, and outcome.

2. Birth trauma, emboli from thrombotic closure of the ductus arteriosus, and thrombosis of the umbilical arteries are discussed as likely causes of this condition.

3. Emphasis is placed on early recognition and vigorous treatment with anticoagulants and vasodilating measures.

4. Conservatism is recommended in the consideration of amputation.

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BACTERIOSTATIC, GERMICIDAL, AND SANITIZING ACTION OF QUATERNARY AMMONIUM COMPOUNDS ON TEXTILES

III. Disinfection of Cotton Fabric

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IN PREVIOUS studies it was demonstrated that a 1:5,000 dilution of some selected quaternary ammonium salts was capable of reducing the bacterial counts to very low levels in test solutions designed to simulate fabric-water ratios of laundry rinse waters. These reductions in count seemed sufficient to indicate a potential value for these compounds at this dilution in improving laundry sanitation.

At dilutions lower than 1:5,000, the counts in the same study were usually reduced to zero indicating that disinfection may have been secured. However, in view of the finding of Roberts[1] that sterile rinse waters cannot be accepted as a reliable index to sterile laundry, it would appear unwise to accept bacterial counts on rinse water or even qualitative data from cultures of rinse water as an absolute index to germicidal or fabric-disinfecting value unless the data can be confirmed by culture of the treated fabric itself.

Obviously a sanitizing process that does not disinfect the fabric itself would have questionable value in preventing the spread of disease by infected cloth and should not be recommended for the treatment of laundry from hospitals, sickrooms, and similar places where specific infectious agents are known or suspected to be present. It seemed important, therefore, in any study evaluating quaternary ammonium compounds for use in laundry sanitation programs to include a rather complete study of their efficiency as disinfectants for the cloth itself. The investigations reported herein were designed to establish for general use an index to the apparent practical disinfecting levels of the five quaternaries used.

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PROCEDURE

As in the previous studies,[2, 3] five quaternaries were employed. They were: (A) para diisobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride; (B) alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride; (C) alkyl (C_6-C_{12}) naphthyl methyl pyridinium chloride; (D) dodecyl acetamido dimethyl benzyl ammonium chloride; and (E) cetyl trimethyl ammonium bromide. These shall be designated henceforth as quaternary A, quaternary B, et cetera.

Escherichia coli was selected as the test organism since it is commonly regarded as the most representative genus of the Enterobacteriaceae and because positive subculture could easily be confirmed by "in vitro" tests.

As reported previously,[3] T.G.E. slants (Bacto Tryptone Glucose Extract Agar) composed of tryptone 5 Gm., glucose 1 Gm., beef extract 3 Gm., agar 15 Gm., and distilled water 1,000

c.c. were used to maintain the organism at 5° C. with monthly transfers, and also for propagation of the cultures for the inocula. One cubic centimeter of a twenty-four-hour T.G.E. broth culture was used to inoculate the surface of Kolle flasks containing 60 c.c. of T.G.E. agar. An aqueous suspension of the organism was prepared by washing with 50 c.c. of distilled water the twenty-four-hour growth from the Kolle slant. Following filtration through Schleicher and Schull paper No. 588, the suspension was diluted sufficiently to give a reading of 50-60 on the Klett-Summerson photoelectric colorimeter, using No. 42 blue filter. A further dilution of 1:20 of this suspension provided a standard inoculum of approximately 10,000,000 bacteria per cubic centimeter.

Two strips of cotton, gauze-type cloth, 5 by 4 inches, weighing 3 grams, were employed as carriers for the test organism. Samples folded to fit two to a Petri dish were autoclaved and dried in a hot air oven. Twelve replicate samples were each inoculated with 2 c.c. of the standardized suspension of *E. coli*. This inoculum approximated a degree of contamination reported in studies of home laundry operations.[4] Two inoculated samples were introduced into each of six pint jars containing 96 c.c. of the dilution of medicant, thus yielding twelve replicate tests for each dilution of disinfectant. The jars were agitated in a launder-ometer for five minutes at the indicated temperatures. Similarly inoculated samples of fabric, agitated in distilled water, served as controls. The ratio of weight of cloth to volume of quaternary was formulated to fall within the wide ranges of fabric-water ratios reportediy used in home and commercial laundry for rinsing operations. The time of exposure, five minutes, also agrees with typical rinsing procedures.

The dilutions of the five medicants employed in the basic study ranged from 1:50 to 1:5,000, or 1 oz. quaternary for 0.094 to 9.4 lb. dry cloth.

Supplemental studies were also made using duplicate cloth samples contaminated with decreasing numbers of organisms prior to exposure to quaternary B at 20° C. for ten minutes, the exposure period recommended by manufacturers of certain quaternaries. The cloth samples were inoculated with 2 c.c. of the standardized cell suspension diluted to provide contaminated cloth characteristic of a variety of conditions varying from that commonly found in the home laundry to a very low level of contamination, such as has been reported in commercial laundries where careful control of temperatures, volumes of water, number of rinses, and other factors are maintained. Thirty-seven suspensions yielding counts from 44 to 10,000,000 cells per cubic centimeter were used in the course of the study. Nine dilutions of medicant ranging from 1:1,000 to 1:50,000 corresponding to 1 oz. quaternary for 1.8 to 93.7 lb. dry cloth were employed.

From investigations made on the degree of bacterial contamination in home and commercial laundries[4] and from data reported by Roberts[1] on fabric liquid distribution of cells, it was believed that 2 c.c. of a suspension containing 10,000,000 bacteria per cubic centimeter would provide test fabrics with a contamination simulating that reported for home laundries where rinse waters possessed an aver-

age count of approximately 300,000 cells per cubic centimeter. Also an equivalent volume of a suspension containing only 1,500 bacteria per cubic centimeter would produce rinse waters containing counts of less than 100 per cubic centimeter, reported to be characteristic of well-operated launderies.

After exposure of the inoculated fabric to the medicant, each sample was removed, expressed of liquid with sterile forceps and introduced into a tube containing 20 c.c. of a 5 per cent distilled water solution of Tamol N,[5] where they were allowed to remain for ninety minutes to assure complete neutralization of the quaternary. The samples were then subcultured in tubes containing 20 c.c. of T.G.E. broth and incubated at 37° C. Tubes were examined for visible growth after twenty-four and forty-eight hours' incubation.

Presence of viable cells on the cultured cloth or in the incubated tubes was determined by transferring the sample of cloth to a Petri dish and covering with Bacto Eosin Methylene Blue Agar (peptone 10 Gm., lactose 5 Gm., saccharose 5 Gm., dipotassium phosphate 2 Gm., agar 13.5 Gm., eosin Y 0.4 Gm., methylene blue 0.065 Gm., per liter), or by merely streaking plates of this medium from the culture tube containing the sample of cloth. The development of colonies displaying the metallic sheen typical of *E. coli* was indicative of survival of the test organism.

RESULTS

The results are presented in Tables I and II and in Fig. 1.

It can be seen in Table I that at 20° C. quaternary A gave no evidence of germicidal activity at dilutions of 1:5,000 or 1:4,000. At 1:3,000 and 1:2,000 one of each twelve tests showed a germicidal effect. The number of tubes showing germicidal action increased progressively as the dilutions were lowered, but disinfection in all twelve tests was not observed at any dilution higher than 1:50. At 45° C., this chemical demonstrated some signs of activity at the 1:5,000 dilution in which one tube showed no viable organisms. This activity increased as the dilution was decreased, but a 1:500 dilution was required to secure sterile fabric in all of the twelve replicate tests.

With quaternary B the results at 20° C. show one sterile sample at 1:5,000, and an increasing number of sterile samples as the dilution was lowered until disinfection was obtained in all twelve tests with a 1:1,000 dilution. Although the number of tests which showed sterile samples with dilutions of 1:5,000 through 1:2,000 was not as great at 45° as at 20° C., disinfection was secured at 1:1,000 regardless of temperature.

No disinfection was apparent at 20° C. with 1:5,000, 1:4,000, or 1:3,000 dilutions of quaternary C. As this quaternary became more concentrated, increasing activity was observed, culminating at 1:100 with a total of twelve sterile tests. When the treatment was at 45° C. this increasing activity with increasing amounts of quaternary became evident at 1:4,000 dilution. Disinfection of all samples was obtained at 1:500 at the higher temperature.

Although some samples were sterile at 1:2,000 with quaternary D at both temperatures, a solution as concentrated as 1:50 did not prevent some organisms from surviving at 20° C. At the higher temperature, some dilu-

tions showed enhanced activity and at 1:50 no organisms survived in the subcultured samples of fabric.

Quaternary E failed to disinfect all the fabric samples at any dilution at either temperature. At 20° C. no evidence of germicidal activity was observed with any dilution until a concentration of 1:250 was used. One sample on subculturing was sterile

The dilutions shown are those which were found to insure disinfection of all twelve replicate samples of cloth inoculated with *E. coli*. In this table the quaternary ammonium salt-dry fabric weight ratios for each disinfecting dilution are included. Consistent germicidal activity was not secured with quaternaries D and E at 20° C. or quaternary E at 45° C., thus

TABLE I. NUMBER OF SAMPLES DISINFECTED BY FIVE QUATERNARIES IN FIVE MINUTES AT TWO TEMPERATURES, FABRIC INOCULATED WITH 10 MILLION CELLS OF *E. coli* PER CUBIC CENTIMETER

TEMPERATURE	QUATERNARY	DILUTIONS								
		1:5,000	1:4,000	1:3,000	1:2,000	1:1,000	1:500	1:250	1:100	1:50
20° C.	A	0	0	1	1	3	6	9	10	12
	B	1	5	7	11	12	12	12	–	–
	C	0	0	0	1	5	10	11	12	–
	D	0	0	0	1	6	10	8	9	11
	E	0	0	0	0	0	0	3	7	–
45° C.	A	1	2	6	8	11	12	–	–	–
	B	0	2	1	7	12	12	–	–	–
	C	0	2	4	6	10	12	12	–	–
	D	0	0	0	4	6	11	11	11	12
	E	0	0	1	2	5	6	8	–	–

TABLE II. APPARENT SAFE DISINFECTING DILUTIONS OF FIVE QUATERNARIES FOR FABRIC INOCULATED WITH 10 MILLION CELLS PER CUBIC CENTIMETER AND TREATED FOR FIVE MINUTES AT TWO TEMPERATURES

QUATERNARY	20° C.		45° C.	
	DISINFECTING DILUTION	RATIO OZ. QUAT.: LB. CLOTH*	DISINFECTING DILUTION	RATIO OZ. QUAT.: LB. CLOTH
A	1:50	1:0.094	1:500	1:0.94
B	1:1000	1:1.8	1:1000	1:1.8
C	1:100	1:0.18	1:500	1:0.94
D	---†	---	1:50	1:0.094
E	---	---	---	---

*The chemical dry fabric ratios are mathematical calculations of the actual dilution used.
†Consistant germicidal activity not secured.

after treatment with 1:3,000 at the higher temperature. Eight from a total of twelve was the maximum number of sterile samples observed at either temperature with this chemical. Due to its insolubility in higher concentrations no further data was obtained.

The data in Table II show the apparent safe, disinfecting dilutions of the five quaternaries for fabric samples when applied at 20° and at 45° C. for five minutes.

no values are given at these points in the table.

In Fig. 1 are shown the results where fabric was inoculated with variable numbers of organisms and subjected to the disinfecting action of quaternary B, alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride, for ten minutes at 20° C. No disinfection of cloth samples was obtained with dilutions from 1:7,500 through 1:50,000 even though as few organisms as 50

per cubic centimeter inoculum were used. Conflicting results were obtained with 1:5,000, the recommended use dilution; hence it was considered unreliable as a disinfectant with the bacterial populations tested.

In contrast, 1:4,000 produced sterile fabric if inoculated with fewer than 1,000 organisms per cubic centimeter but was either unreliable or ineffective with greater numbers of cells.

A dilution of 1:3,000 effectively eliminated the viable organisms in an inoculum containing 50,000 cells, but with populations up to 500,000 contradictory results were obtained and this dilution did not disinfect cloth harboring cells in excess of this figure. Disinfection was obtained with 1:2,000 when the fabric was inoculated with populations up to 100,000 but greater numbers of organisms gave contradictory results. A 1:1,000 dilution of quaternary B at 20° C. in ten minutes disinfected the fabric heavily contaminated with a suspension containing 10 million organisms per cubic centimeter. This effectiveness was also observed when fabric was exposed for five minutes as shown in Tables I and II.

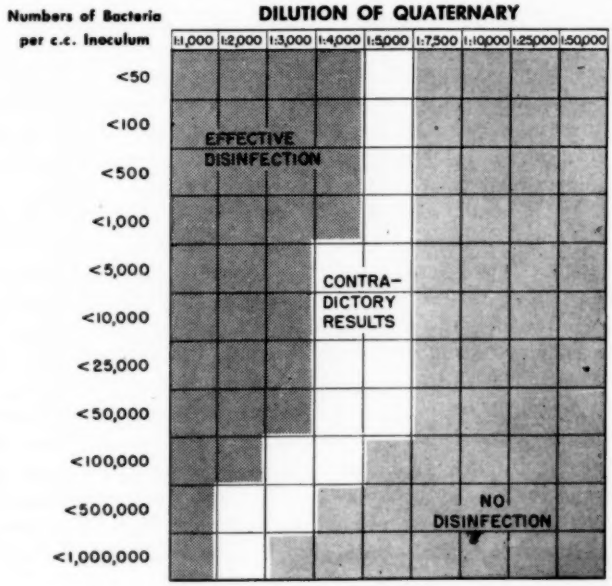

Fig. 1.

DISCUSSION

The data show clearly that in the use of these quaternaries, concentrations considerably greater than those necessary to impart bacteriostatic properties to the fabric itself, or to reduce the bacterial counts of rinse waters to significantly low levels as shown in previous reports,[2, 3] are necessary to assure disinfection of the fabric itself, at least where the fabric carries any appreciable number of bacterial contaminants. To illustrate, at 45° C.,

in a dilution of 1:100,000 quaternary A, when adsorbed on fabric, was bacteriostatic against *Proteus mirabilis,* for sixteen hours, six hours over the control;[2] a 1:5,000 dilution sanitized fabric inoculated with *E. coli,*[3] whereas in this study a dilution of 1:500 was required to disinfect fabric contaminated with *E. coli.*

The results do indicate, however, that where the bacterial contamination is at very low levels, higher dilutions of quaternaries may be effective for use as germicidal sanitizing rinses. As judged by the results with quarternary B where a dilution of 1:4,000, or a chemical-dry fabric ratio of 1 oz. quaternary to 7.5 lb. of cloth, seemed to be effective as a germicidal sanitizer for fabric carrying fewer than 1,000 organisms per cubic centimeter, it would seem that the effective dilution levels for this use may be only slightly lower than the 1:5,000 dilution that was indicated by rinse water counts to have sanitizing values.

Chemical germicides are commonly expected to act in the absence of added heat. Thus, evaluations of these products as disinfectants for fabrics must be based primarily on the results found at 20° C. It should be noted, however, that the disinfecting values of quaternaries A and C were materially enhanced by increasing the temperature from 20° to 45° C., whereas that of the apparently more effective product, quaternary B, was not thus increased. From this it would seem that with quaternaries A and C, at least, the rinse temperature might control the results secured at dilutions lower than 1:5,000.

The data in these studies show that considerably lower dilutions of these products are necessary to secure reliable disinfection of fabric than are commonly recognized as bactericidal for other uses. This may be due in part to competitive adsorption between the fabric and the bacteria for the quaternary ammonium salt in the test solution.

The wide differences in the relative values found for the five products examined show clearly that it is practically impossible to draw any general conclusion relative to the disinfecting efficiency of compounds of this class for any specific use and that each individual chemical must be evaluated according to the purpose for which it is recommended.

It is believed that the constant volume of the dilutions of disinfectants used is of a magnitude which assured a uniform application of the chemicals to the weight of fabric employed. However, the reliability of the chemical-fabric weight ratio for use as an index in laundry procedures where different volumes of rinse waters are employed has not been established.

The very wide differences between the levels of these products necessary to impart residual bacteriostatic properties to cloth, to secure a sanitizing effect and to secure reliable disinfection of the cloth itself, would seem to make it essential for the manufacturers to define clearly the purposes for which the product may have value in home and commercial uses, and the specific conditions under which these values may be secured.

It is believed that the safe sanitizing levels with these chemicals will correspond closely with the levels recorded as "contradictory results" in Fig. 1. If so, this figure indicates that the concentration necessary to sanitize increases as the contamination increases

in the same manner shown in disinfection.

SUMMARY

Five typical quaternaries have been studied in an attempt to ascertain the conditions necessary for disinfection of cloth inoculated with bacterial populations of *E. coli* comparable to the numbers of organisms found in the final rinse water of heavily contaminated laundry. One product tested did not disinfect fabric under any conditions in these tests and another failed to provide for disinfection at 20° C. With those which did disinfect, it has been found that dilutions ranging from 1:50 to 1:1,000 are necessary. The quaternary—dry cloth ratio of this range of dilutions is from 1 oz. quaternary for 0.094 to 1.8 lb. of dry cloth. In general, the five quaternaries were more efficient at 45° than at 20° C.

Quaternary A, para diisobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride, disinfected fabric in a dilution of 1:50 at 20° C. but only 1:500 was required at 45° C. These provide ratios of 1 oz. quaternary to 0.094 and 0.94 lb. of fabric, respectively. With quaternary B, alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride, a dilution of 1:1,000, 1 oz. quaternary to 1.8 lb. cloth, was effective at both 20° and 45° C. Disinfection was secured with quaternary C, alkyl (C_6-C_{12}) naphthyl methyl pyridinium chloride, at 1:100, 1 oz. quaternary to 0.18 lb. fabric, at 20° C. and at 1:500 at 45° C. Quaternary D, dodecyl acetamido dimethyl benzyl ammonium chloride, failed to disinfect at 20° C. in any dilution, but at 45° C. disinfection was accomplished at 1:50. No disinfecting dilution was obtained for fabrics with quaternary E, cetyl trimethyl ammonium bromide, due, in part, to its low solubility.

It was found that quaternary B disinfected more efficiently as the numbers of organisms in the inocula decreased. The dilution necessary to disinfect fabric contaminated with numbers of cells comparable to conditions found in rinse waters of commercial laundries was 1:4,000 or 1 oz. quaternary to 7.5 lb. of dry cloth. When the contamination was in the order that might be expected to represent rinse waters in home conditions, the effective dilution was 1:1,000 or 1 oz. quaternary for 1.8 lb. of dry fabric.

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Symposium on Cerebral Palsy
Part III

EARLY DETECTION OF CEREBRAL INJURY

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SWIFT advances of modern medicine leading to rapid conquest of acute diseases only accentuate problems posed by chronically handicapping conditions. In an era characterized by almost daily discoveries of major importance it is apparent how painfully slow is progress in unraveling the complexities of many chronic disorders, of which cerebral palsy is a challenging example. It is a disease often characterized by obscurity of etiology, uncertain methods of prevention, difficulties in evaluation, necessity for meticulous and prolonged therapy of an integrated type, frequently with only partial success, and presenting psychologic and socioeconomic problems of first magnitude.

Although present efforts, both lay and medical, to expand diagnostic and therapeutic services to children who have cerebral palsy are eminently worth while, the most practical approach is through coordinated research which seeks to determine etiology, thereby possibly leading to preventive measures. It is this aspect of the disease toward which this paper is directed, particularly the early detection of cerebral injury in the newborn period. Diagnosis of cerebral injury after the neonatal period will not be discussed.

Cerebral palsy results from prenatal, natal, or postnatal factors which damage the brain to produce neuromuscular dysfunction. In the proceedings of the first symposium presented under the auspices of the United Cerebral Palsy Association, Wolf[1] ably reviewed possible factors in etiology. Although one is impressed with what is actually known concerning pathogenesis of the condition, it is obvious that in many respects ignorance is extensive, if not abysmal. Nevertheless, it is in the field of prevention that the best hope of progress lies, and this implies a better understanding of etiology.

It is the purpose of this paper to consider the etiological role of deleterious factors operating during labor and delivery, realizing that such events account for only a portion of the victims of cerebral palsy. The thesis is: (1) birth damage to the brain occurs more commonly than generally suspected; (2) ordinary clinical observation may fail to detect minimal damage; (3) electroencephalography is a useful diagnostic adjunct; (4) careful correlation with factors present during labor and delivery may clarify the cause of damage, this possibly leading to obstetric refinements which may make child-

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birth safer for the child; (5) long-term follow-up observations are indicated to ascertain the relationship of birth damage to residual disabilities such as cerebral palsy or other neurological defects, recurrent convulsive seizures, mental retardation, or abnormalities of behavior. Although injury at birth is stressed, it is important to remember that many infants who have clearly sustained intracranial damage survive without residual disability,[2] and, conversely, some who in the neonatal period fail to exhibit evidence of injury subsequently show unmistakable signs.

METHOD OF STUDY

In an effort to determine the frequency of birth injury to the brain and the aftereffects, a project was started several years ago in the Pediatric Division of the University of Tennessee. In addition to evaluation of pregnancy, labor, delivery, and clinical condition of the infant in the newborn period, electroencephalograms were obtained at frequent intervals in the first days of life and in serial follow-up observations. Although Smith[3] and Lindsley[4] had previously described electroencephalographic patterns of newborn infants, the number of babies studied was so small that more extensive investigations were indicated in order to determine normal patterns to serve as a foundation for subsequent intrepretations of abnormal records. In a series of normal babies born of mothers whose pregnancy, labor, and delivery were uneventful, and who had received no drugs, electroencephalograms were obtained in various states of alertness ranging from wide awake through drowsiness to sleep.[5, 6, 7] Both full-term and premature infants were studied. The next investigative phase was the determination of the effects on the baby's brain potentials of drugs given to the mother during labor and delivery.[8, 9] The great majority of the 400 newborn infants who have now been studied electroencephalographically and clinically fall in these normal groups born with, and without, the use of obstetric analgesic or anesthetic agents.

In the course of the basic studies on normal infants a small group of abnormal babies was evaluated clinically and electroencephalographically.[10] More recently, the project has been directed almost entirely toward the study of infants born of mothers in whom there was known abnormality during pregnancy, labor, or delivery, or babies who were themselves abnormal in the newborn period. Due to the recent nature of these studies, insufficient time has elapsed to permit adequate longitudinal studies of each infant. However, in this group of infants weighted toward abnormality, many have shown evidence of brain damage, a far higher percentage than in infants selected at random.

There are several possibilities when the brain of an infant is damaged in the birth process: (1) death; (2) full recovery; (3) residual disabilities, some of which occur in combinations, including (a) cerebral palsy and other neurological defects; (b) recurrent convulsive seizures; (c) mental impairment; (d) distortion of personality on an organic basis. In the longitudinal studies of the infants included in the series specific attention is given to presence or absence of residual disabilities cited above, in

the hope of determining more accurately the frequency with which such handicaps follow known brain damage at birth.

The literature is replete with reports of intracranial damage incurred at birth in which the diagnosis was made in retrospect, often years later. Although in many instances the history clearly indicates severe damage, the causes of birth injury are entirely too complicated, and sometimes subtle, to permit consistently accurate evaluation long after delivery. Therefore, the attempt has been made in this project to determine at time of occurrence factors which might result in damage to the fetus during labor and delivery.

In addition to identifying data for each mother and infant, the following information is obtained: (1) gravida; (2) para; (3) pregnancy (normal, abnormal); (4) data on labor and delivery, including length of first stage, length of second stage, intensity of labor, any abnormalities such as bleeding; highest and lowest blood pressures; slowest fetal heart rate; presentation; type of delivery; drugs used during labor, dosage, time before delivery; anesthetic agent, if any, name of agent, minutes given; pain relief to mother prior to anesthesia or nerve block; (5) data on newborn baby, including weight, whether respiration is spontaneous or delayed and extent of delay; method of resuscitation, if any; clinical condition of infant, including alertness, type of respiration, presence of neurological abnormalities, or signs of cerebral damage.

In each instance, labor and delivery are evaluated from the standpoint of factors which might produce fetal anoxia or hemorrhage, such as: (1) maternal hypotension; (2) maternal hypertension, with presumed peripheral arteriolar spasm which might impair placental blood flow; (3) poor maternal oxygen transport, due to pneumonia, severe anemia at delivery, cardiac decompensation, or anesthetic mixtures containing insufficient oxygen; (4) uterine conditions, such as placenta previa, premature separation of the placenta, or uterine tetany; (5) abnormalities of the cord, including prolapse of the cord, cord wrapped tightly about the infant's neck or other parts, or holding the infant's head back when crowning; (6) factors which might exercise a traumatic effect on the fetal brain, or result in hemorrhage or anoxia, including unusually prolonged or difficult labor, tumultuous rapid labor, breech delivery, cephalopelvic disproportion, rotation, version, use of forceps other than low forceps with episiotomy, and birth by cesarean section; (7) whether the infant appears narcotized or in shock. Maternal blood pressure is followed carefully, and the duration of hypotension below 100 mg. Hg systolic is noted. The fetal heart rate is observed for slowing, and the slowest fetal heart rate and duration of fetal bradycardia are recorded.

All of these data on labor and delivery are correlated with clinical condition of the infant and electroencephalographic findings in an attempt to determine at the time of birth and in the early neonatal period whether or not damage to the brain has occurred. Thus, the program stresses collection of data at the time deleterious events occur, in the realization that diagnosis of damage in retrospect is notoriously inaccurate.

As soon as possible after birth the initial electroencephalogram is obtained. Subsequent electroencephalograms and clinical evaluations are performed at daily intervals as long as the baby is in the hospital, usually only a few days. Infants are then brought back for longitudinal follow-up studies at intervals of three to six months, at which time an additional electroencephalogram is obtained and the patient is examined with particular reference to growth and development, occurrence of neurological defect, convulsive seizures, apparent mental retardation, abnormalities of behavior, or any new event which might have damaged the brain.

The technique for obtaining electroencephalograms in newborn infants is as follows, and represents a modification of methods described in previous communications:

Electroencephalograms are obtained in a room near the nursery. Precautions for aseptic technique are employed. Tracings are obtained as soon after birth as possible, and thereafter, on following days, within sixty to ninety minutes after feedings, in order to allow the baby to rest from the nursing process, and yet not permit enough time to elapse for the blood sugar to reach hypoglycemic levels. Most of the infants did not receive oxygen therapy at the time of tracing. If it is necessary to continue administration of oxygen during the tracing, the duration and amount of oxygen given are noted on the record. Tracings are obtained in stages of alertness from wide awake through drowsiness to sleep with every attempt made to have a continuous record and an arousal period at the end of the tracing. The machine used is an eight-channel electroencephalograph made of two Offner (Type C 144) four-channel crystograph electroencephalographs joined to a common calibrator and switch. Standard measures are employed to assure valid tracings. After the scalp has been cleaned with acetone and prepared with electrode jelly, lightweight solder disks are applied with bentonite paste. The electrode is covered with nonelastic collodion and dried with a fine stream of compressed air. Infants are usually left in the incubator or placed on the bed. They are rarely held, although on occasion it has been necessary to hold some infants to reduce muscle artifact. Tracings are obtained from both scalp-to-ear and scalp-to-scalp leads. Tracings are usually recorded from all leads (two frontal, two parietal, two occipital, two temporal) to both ears, to the left ear and then to the right ear. Tracings are obtained between scalp electrodes as follows: frontal to parietal, parietal to occipital, occipital to temporal, and temporal to frontal. Another standard recording is frontal to parietal, parietal to temporal, temporal to occipital, and occipital to frontal. When an abnormality is observed in any locality, more detailed and specific triangulation methods are employed.

The difficulty in interpreting the data obtained in the manner mentioned above lies in the fact that several factors may be simultaneously responsible for damage incurred. For example, a woman given caudal analgesia may develop precipitous hypotension which fosters fetal anoxia, and at the same time may have cephalopelvic disproportion which encourages intracranial hemorrhage. In another case, premature separation of the placenta may be associated with a long, hard labor, or prolapse of the cord. Endless combinations of deleterious factors thus exist which often defy neat analysis. Yet if anything is to be learned which will lead to possible preventive measures, each in-

jurious event deserves an attempt at clarification. The situation is further complicated by the fact that infants born of obviously abnormal labor and delivery may, themselves, be clinically normal, whereas some whose birth has seemed entirely uneventful may show signs of damage.

CASE STUDIES

Although our data are not yet sufficiently extensive to justify conclusions concerning frequency of birth damage of the brain, the following case studies of infants known to have sustained such injury illustrate points brought out in the above remarks.

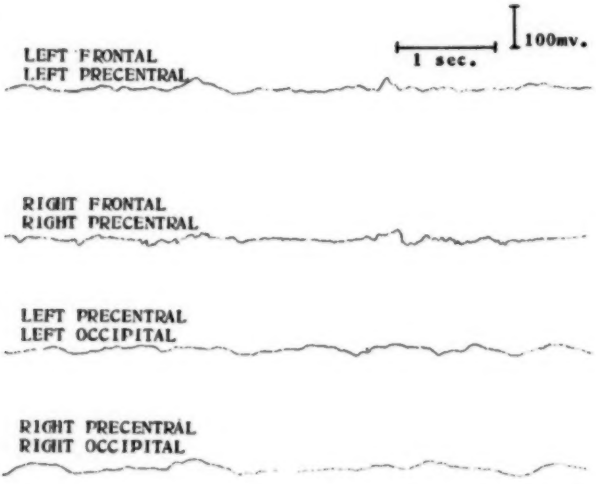

Fig. 1.—EEG obtained on an infant 24 hours old, awake, revealing marked suppression of activity in all areas.

CASE 1.—Previously reported.[10(Case 1)] Because of cephalopelvic disproportion in a primiparous mother the delivery of this infant from a right occipitotransverse position was exceptionally difficult. The infant was in critical condition at the moment of birth and required extensive resuscitative measures. In the first twenty-four hours the following abnormalities were noted: feeble whining cry, at times changing to sharp and high-pitched (cephalic cry); cyanosis; bulging fontanel; opisthotonus; hemorrhage into anterior chamber of right eye; dyspnea with retraction of the thoracic cage; bloody mucus in air passages; overriding of bones at right parietal eminence.

An electroencephalogram obtained when the infant was 24 hours old revealed marked suppression of activity in all leads (Fig. 1). Death occurred 40 hours after birth. The clinical diagnosis of widespread intracranial hemorrhage was substantiated at post-mortem examination, which showed subarachnoid hemorrhages over both sides of the cortex with extreme congestion of cortical vessels. As clinically suspected, pulmonary hemorrhages were noted as well as extensive atelectatic areas and areas of emphysema.

This case illustrates electroencephalographic changes in a case of subarachnoid hemorrhage, caused by birth trauma. Diminution of cortical

potentials may have resulted either from the damping effect of the overlying blood, or from devitalization of the cortical cells incident to the hemorrhage and associated prolonged anoxia.

CASE 2.—The mother of this infant was in severe pre-eclampsia, with a blood pressure on admission of 180/110 mm. Hg. Spontaneous breech delivery had started in the ambulance on the way to the hospital. Upon arrival at the hospital, the head was still in the birth canal, and it was determined that fifteen minutes had elapsed between birth of the body and delivery of the aftercoming head. The infant failed to breathe spontaneously for fifty minutes, requiring resuscitative measures. In the twenty-six hours before death the following abnormalities were noted: irregular respiration; marked lethargy; weak cry; cyanosis; bilateral spasticity; increased deep tendon reflexes; hyperactive Moro reflex; impaired grasp reflex; bloody mucus in pharynx.

An electroencephalogram obtained fifteen hours after delivery (Fig. 2) revealed seizure patterns beginning with either a 2.5 per second spike and wave or multiple spiking usually beginning over the left parietal region, but being sharper and higher in both temporal areas. There was a spread to all areas, less prominent over the frontal region. Low microvoltage mixed frequency episodes appeared, usually shorter over the left parietal area. There was a shifting of abnormal activity; however, it was dominant on the left and correlated well with the clinical focus.

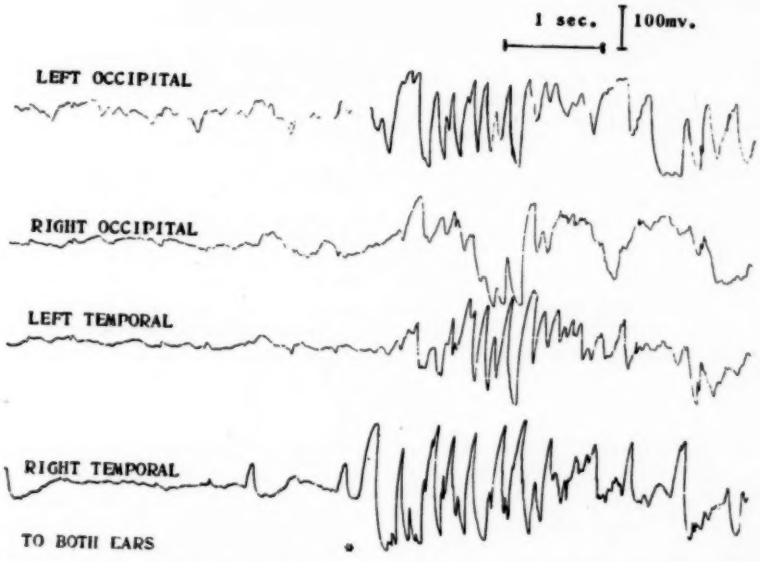

Fig. 2.—EEG obtained on an infant 15 hours old, awake, revealing suppression of activity followed by seizure pattern of high microvoltage slow and fast spikes in all areas, dominant to the left, higher and sharper over both temporals.

Post-mortem examination revealed hemorrhagic areas in the Sylvian fissures bilaterally.

This case illustrates electroencephalographic findings in a patient with bilateral cerebral hemorrhage due to a markedly difficult labor accom-

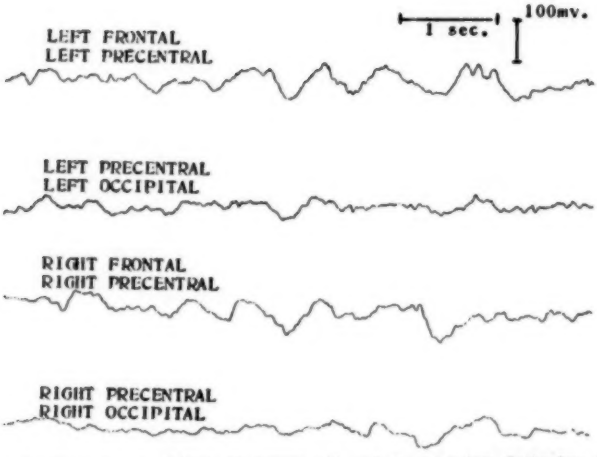

Fig. 3.—EEG obtained on an infant 40 hours old, asleep, showing flattening over the right precentral-occipital area, indicating a possible focus of pathology in that region.

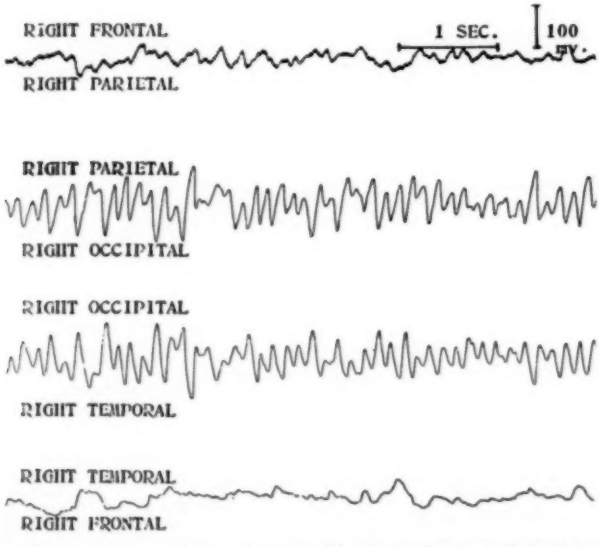

Fig. 4.—EEG (awake) on 3-year 9-month-old child who had brain damage at birth, showing localized episodic slow activity over the right parietal and occipital areas. The corresponding area of the left hemisphere was normal.

panied by factors producing extreme anoxia of the brain, and probable impairment of intracranial circulation. The role that maternal preeclampsia may have played in creating anoxia, particularly significant hypertension with probable peripheral arteriolar constriction, cannot be fully ascertained.

CASE 3.—Previously reported.[10(Case 7)] This baby was born of a mother who developed precipitious hypotension during caudal analgesia. Labor and delivery were otherwise uneventful. When caudal analgesia was instituted, the maternal blood pressure was 154/98 mm. Hg. Thirty-five minutes later it had risen to 168/110. Hypotension then rapidly developed to a level of 82/70 mm. Hg. For a period of ten minutes the maternal blood pressure remained within a range of 82 to 100 mm. Hg systolic and 70 mm. Hg diastolic. During a part of this period the systolic pressure was well below 90 mm. Hg. Oxygen and ephedrine were administered and the pressure rose to normal levels.

The infant appeared normal at birth and for the first four days of life. He then developed marked tremors of the left arm and leg which lasted only thirty seconds. He was removed from the nursery without medical approval.

When the baby was 40 hours old, two days before onset of tremors, an electroencephalogram was obtained (Fig. 3) which revealed flattening over the right precentral-occipital region, indicating a possible focus of pathology in the area.

Follow-up observations over a period of three years nine months revealed perfectly normal growth and development, and an intelligence quotient of 100. However, an electroencephalogram obtained at this age (Fig. 4) showed localized episodic slow activity over the right parietal and occipital areas. The corresponding area of the left hemisphere was normal. This tracing is of interest in showing the persistence of an abnormal electroencephalogram in a child who had brain damage at birth but is now normal.

This case is of interest in three respects: (1) maternal hypotension apparently resulted in inadequate placental blood flow which produced temporary fetal anoxia, resulting in cortical damage with clinical and electroencephalographic abnormalities in the newborn period; (2) electroencephalographic abnormalities antedated by two days clinical evidence of nervous system damage; (3) in spite of complete clinical recovery, abnormalities of brain potentials persist. The fact that electroencephalographic alterations can appear two days before clinical abnormalities naturally suggests that cases may well occur in which only the electroencephalogram will reveal evidence of brain damage. How often subclinical damage of this type occurs is, at present, entirely conjectural.

CASE 4.—Previously reported.[10(Case 2)] This infant was delivered of a primiparous mother after a thirty-six-hour apparently normal labor and delivery. Respirations were delayed and resuscitation was required. Recurrent bouts of cyanosis occurred in the first hours, associated with a feeble, listless appearance. Repeated generalized convulsive seizures began at twenty-one hours, and recurred for a period of two days. Gross tremors persisted for nine days, after which the infant appeared normal.

The first electroencephalogram (Fig. 5) obtained at 16 hours of age, five hours prior to onset of convulsions, revealed phase reversals in the left frontal-precentral and left precentral-occipital tracings, indicating a localization of cortical abnormality in the left precentral area.

Follow-up observations to the age of 3 years 10 months revealed apparently normal growth and development, with the exception that the intelligence quotient is 80. Siblings

and other members of the family were not tested. A point of interest, indicating the need for continuous evaluation of intercurrent factors which might produce brain damage, is the fact that the child was in an automobile accident at the age of 16 months and was unconscious for one hour. It now becomes difficult in subsequent studies on this child to separate the effect of birth damage from possible acquired traumatic injury.

The electroencephalogram at 3 years 10 months of age revealed generalized irregular slow activity, more evident in early sleep, with marked asymmetry of the hemispheres, the left being more abnormal.

CASE 5.—Previously reported.[10(Case 6)] This full-term infant was delivered of a toxemic mother who became disoriented. There was considerable difficulty in delivering the shoulders, and the cord was wrapped tightly around the neck. It had to be cut to deliver the infant. The baby required resuscitation, was deeply cyanotic, exhibited marked spasticity and opisthotonus, and had a shrill high-pitched cry. Tremors were noted the first day, but no convulsions were observed. He was discharged from the nursery at 9 days of age, much improved.

An electroencephalogram (Fig. 6) obtained at 24 hours of age revealed episodic slow activity, more intense over the anterior regions.

Follow-up observations to the age of 3 years 3 months revealed entirely normal growth and development, and the intelligence quotient at this time was 93. We have not determined the intelligence quotients of siblings and parents to ascertain if a value of 93 is low for this family. However, the electroencephalogram (Fig. 7) showed generalized slow activity, maximal over the left parietal region.

This case illustrates that an infant severely damaged at birth may still recover completely from a clinical standpoint. However, the persistence of electroencephalographic abnormalities is of interest.

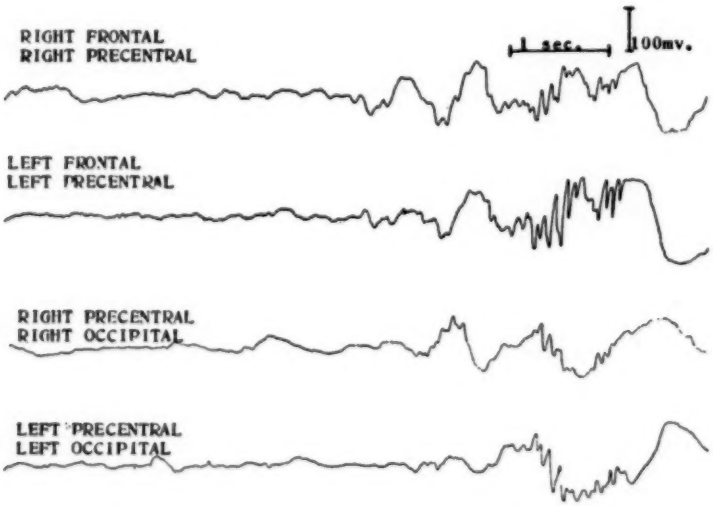

Fig. 5.—EEG obtained at 16 hours of age on a sleeping infant, five hours prior to convulsions, showing phase reversals over the left precentral area, indicating a localization of pathology in that region.

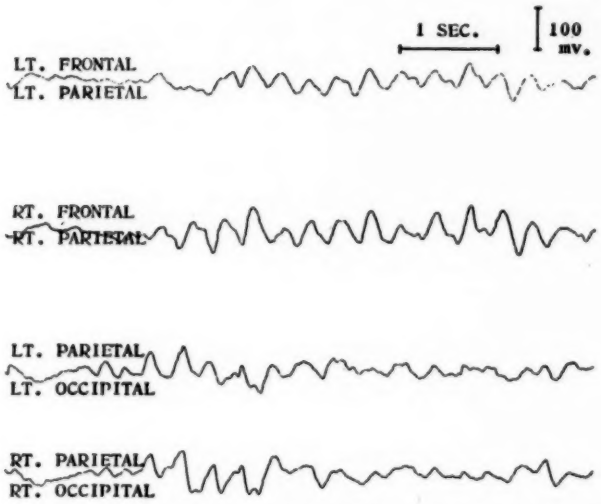

Fig. 6.—EEG on an infant 24 hours of age, revealing episodic slow activity, more intense over the anterior regions.

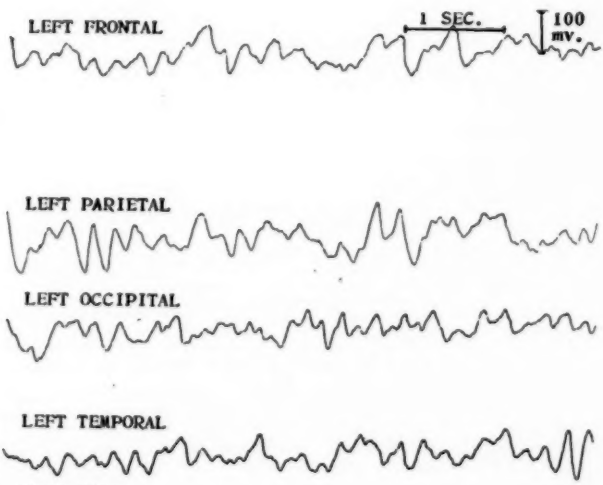

Fig. 7.—EEG (awake) on 3-year 3-month-old child who had brain damage at birth, showing generalized slow activity maximal over the left parietal region.

CASE 6.—Previously reported.[10(Case 4)] This full-term infant was delivered of a primiparous mother by high forceps, there being considerable cephalopelvic disproportion. The infant appeared normal at birth and for twenty-four hours, but on the second day developed rotary nystagmus and generalized convulsions, followed by generalized spasticity which slowly disappeared. He was discharged from the nursery appearing normal on the tenth day.

An electroencephalogram at this time showed slow, high microvoltage, spiked waves, maximal over the left parietal-temporal region.

CASE 7.—Previously reported.[10(Case 8)] This infant was the second of twins, having been delivered fifteen minutes after the first from a shoulder presentation by version and breech extraction. He seemed normal at birth and thereafter during his stay in the nursery.

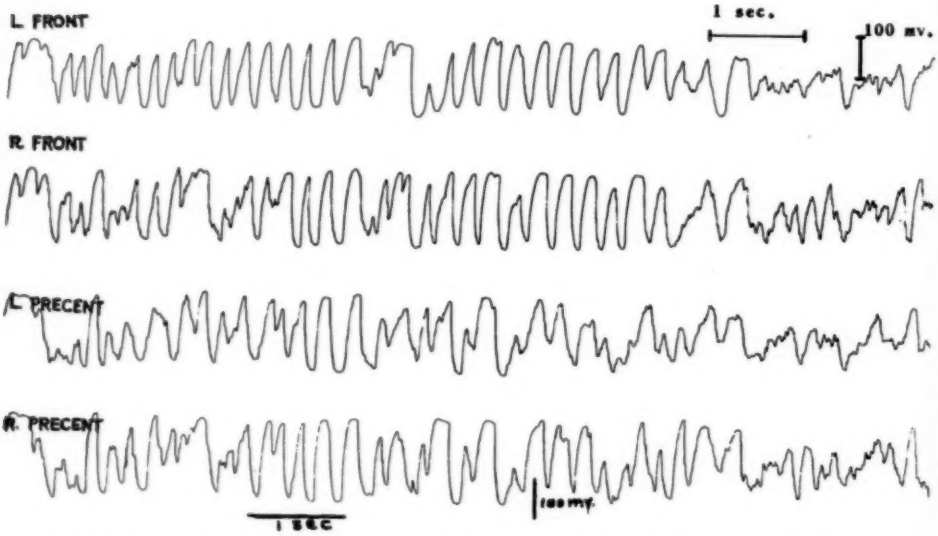

Fig. 8.—EEG obtained on an infant 24 hours old at time of generalized convulsions, showing slow, high microvoltage activity in all areas.

An electroencephalogram was obtained when the infant was 24 hours old (Fig. 8) at the time of generalized convulsions, more marked on the right. Spike wave activity was present, dominant over the left hemisphere.

Follow-up observations to the age of 3 years 10 months revealed a normal child, with the exception of an intelligence quotient of 76 and the presence of a speech defect. Siblings and parents were not tested for level of intelligence.

An electroencephalogram obtained at 5 days of age revealed deep suppression over the right hemisphere.

Follow-up observation for a period of three years five months revealed a clinically normal child with an I.Q. of 80. The twin's I.Q. was 83, illustrating the importance of testing siblings of patients being evaluated.

An electroencephalogram at this age showed generalized slow activity, maximal over the right occipital region. This case illustrates possible subclinical cortical damage incurred

in an apparently normal labor and delivery, although the effect of an adverse influence, such as genetic defect or acquired prenatal damage, acting before labor and delivery, cannot be excluded. Further, it illustrates the value of electroencephalography, as contrasted with mere clinical observation, in determination of cortical abnormality.

In none of the cases cited above was cerebral palsy a residual complication of birth damage. Although electroencephalograms were not obtained in the newborn period, in the following four cases cerebral palsy appears clearly related to birth damage. Some of these children were born elsewhere and some before our studies on electroencephalography of the newborn infant were instituted. It is recognized that in these cases diagnosis of birth damage is being made in retrospect, but the evidence seems conclusive.

CASE 8.—This infant was born after a short two-hour labor, the eighth child of a multiparous mother. The cord was wrapped twice around the child's neck. She was cyanotic at birth, and required resuscitative efforts for five minutes before spontaneous respiration was established. She nursed poorly in the newborn period, and had to be fed by dropper. Gross convulsive jerkings of the left leg were noted in the early neonatal period. Development was retarded, the child not sitting alone until 1 year of age, walking at 3 years, and talking at 3½ years. At 9 years of age, she walked poorly, talked almost incoherently, and continued to have convulsive seizures every two to three months. She was considered to be a definite case of cerebral palsy with recurrent convulsions resulting from marked anoxia during labor and delivery.

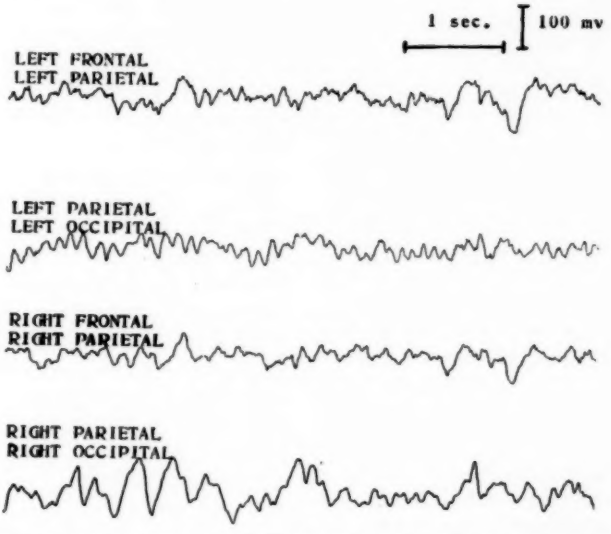

Fig. 9.—EEG obtained on an 8-year-old child with definite cerebral palsy showing marked slowing over the right parieto-occipital region, with a spread of slow activity to the left parietal area.

An electroencephalogram (Fig. 9) taken at 8 years of age showed marked slowing over the right pari-

eto-occipital region, with a spread of slow activity to the left parietal area.

CASE 9.—This infant was born after a difficult labor which resulted in tearing and prolapsing of the cord. Respiration was spontaneous, but the cry was weak. The infant continued to be cyanotic and required oxygen constantly for ten days. Swallowing was difficult, the sucking reflex was impaired and feedings were given by dropper. The child was never able to sit or stand alone. He was thought to have suffered intense anoxia during delivery, with resultant widespread damage to the brain eventuating in cerebral palsy.

An electroencephalogram taken at 4 years of age showed slowing in all areas, dominant in the right hemisphere.

CASE 10.—This infant was born after a labor of three days' duration. Convulsions began in the newborn period and continued to occur frequently thereafter. Development in sitting, walking, and talking was markedly retarded. The head was abnormally small, deep tendon reflexes were hyperactive, and there was spasticity of both arms and legs. This patient was considered to have sustained brain damage in the birth process, which resulted in probable cerebral atrophy and impaired growth of the brain, associated with recurrent convulsive seizures, mental impairment, and cerebral palsy.

An electroencephalograph taken at 13 months of age showed marked asymmetry of the hemispheres, with slow activity dominant on the left, and relatively no activity on the right.

CASE 11.—This infant was delivered by cesarean section after 72 hours of labor. Respiration was delayed. Convulsions occurred in the newborn period and thereafter to 4 years of age. An examination at this time revealed marked mental retardation and inability to speak. The left arm and leg were spastic. A ventriculogram showed hydrocephalus, with dilatation of all ventricles (right lateral larger than left lateral ventricle) and diffuse atrophy of the brain.

The child was considered to have suffered brain damage in the birth process, resulting in diffuse atrophy and hydrocephalus, which eventuated in recurrent convulsive seizures, mental retardation, and cerebral palsy.

An electroencephalogram taken at 18 months of age showed irregular slow activity of high amplitude in all areas.

CLINICAL EVIDENCE OF INTRACRANIAL DAMAGE IN THE NEWBORN PERIOD

Although many infants who sustain birth damage exhibit unmistakable signs, some give only suggestive evidence. In general, the following abnormalities, occurring in various combinations, suggest cerebral injury: (1) undue apathy or restlessness; (2) otherwise unexplained pallor or cyanosis; (3) respirations more irregular than is customary for the newborn infant; (4) feeble, whining cry, often interspersed with a sudden shrill cry; (5) poor nursing, disinterest in feedings, and impaired swallowing; (6) vomiting; (7) rapid pulse if shock is present, or slow pulse if intracranial pressure is elevated; (8) unexplained variations in temperature; (9) disappearance of the Moro reflex, which may return days later; (10) ocular signs, including strabismus, nystagmus, dilation of pupil; (11) in certain cases, bulging of fontanel; (12) twitchings, tremors, convulsions, spasticity, opisthotonus.

If hemorrhage has occurred and the blood has entered the subarachnoid space or the ventricular system, the presence of blood may be revealed by lumbar puncture, bilateral subdural taps, or ventricular punctures. Evidence that such blood resulted from previous hemorrhage, and not from

trauma caused by the tap, is revealed by crenation of red cells when examined immediately, xanthochromia of the supernatant fluid when the material is centrifuged, and elevated protein content of the supernatant fluid. Later, pneumoencephalography may be utilized to reveal in some cases cortical atrophy and ventricular dilatation resulting from destruction of brain tissue.

Emphasis on electroencephalographic abnormalities in the detection of cerebral damage by no means implies that clinical observation plays a secondary role. The two should be weighed together. However, in some few instances, as indicated above, the electroencephalogram may reveal subclinical damage.

DISCUSSION AND SUMMARY

The preceding discussion has emphasized the multiplicity of factors which may result in damage to the brain of the infant, sometimes resulting in subsequent cerebral palsy. Stress has been laid on full-scale evaluation of pregnancy, labor, and delivery to ascertain as exactly as possible the cause or causes of damage. If etiology can be evaluated more fully it is only logical to suppose that refinements in management of pregnancy, labor, and delivery may lead to diminution in the number of children who suffer cerebral palsy as the result of such injuries. However, the adventure of being born is so innately hazardous that even the most perfect management of pregnancy, labor, and delivery cannot be expected to prevent all cases of cerebral damage.

Although careful clinical observation usually suffices to detect early cerebral damage, a more sensitive technique, such as electroencephalography of the newborn infant, aids in the detection of subclinical damage.

Prolonged follow-up observations are indicated in children known to have sustained cerebral injury as a result of deleterious factors during pregnancy, labor, or delivery. Specific attention should be directed toward the four chief residual disabilities: (1) cerebral palsy and other neurological defects; (2) recurrent convulsive seizures; (3) mental retardation; (4) abnormalities of behavior resulting from organic damage of the brain. In such longitudinal studies, intercurrent events, such as head trauma, intracranial infections, and episodes of asphyxia which may occur accidentally or from severe illnesses, should be carefully evaluated and recognized as possible causes of brain damage.

Integrated research efforts of obstetricians, pediatricians, neurologists, neurosurgeons, psychometrists, and child psychiatrists should be directed more fully toward the problem of brain damage of the newborn infant. The obstetrician and pediatrician should no longer regard the severance of the umbilical cord as a symbolic separation of the specialties.

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OBSERVATIONS ON SOME CAUSES OF CEREBRAL PALSY BASED ON POST-MORTEM FINDINGS IN NEWBORN INFANTS

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ALTHOUGH grossly demonstrable cerebral lesions are well recognized as a cause of neonatal death, the importance of certain cerebral lesions sustained before or during delivery as a cause of neurological disorders in later life is less well recognized. Because of technical difficulties encountered in examining the brain of infants dying during the neonatal period, the absence of gross intracranial lesions is often erroneously interpreted as indicating the absence of cerebral changes. Furthermore, few or no histologic alterations may occur in the brains of infants dying as a result of a brief period of intrauterine anoxia. Therefore, the frequency with which cerebral damage occurs in infants dying shortly after delivery is often underestimated.

The present paper is not intended to be a statistical survey of the manifold causes of cerebral palsy. Instead it is offered in an attempt to stimulate interest in the pathologic findings in the central nervous system of infants dying during the neonatal period, and through this, a better understanding of the pathogenesis of cerebral palsy.

Pathologic findings are commonly present in the central nervous system of infants dying during the neonatal period. In a series of 100 complete autopsies performed on infants dying during the neonatal period,[1] death was attributed to a lesion in the central nervous system in thirty (Table I).

Moreover, in the remaining seventy infants there were seventeen in whom definite intracranial lesions were thought to represent contributory rather than primary causes of death (Table II). Multiple lesions were present in the central nervous system of some of these patients.

Thus, significant intracranial lesions were present in almost one-half of the patients in this series, yet in one-third of the infants in whom intracranial lesions were present these were not thought to be the primary cause of death. Therefore, it would seem probable that comparable lesions might exist in some infants who survive the neonatal period, and might be responsible for some of the neurological disorders observed in older infants and children.

Intraventricular hemorrhage as a cause of neonatal death is seen principally in premature infants.[2, 3, 4] The source of the bleeding is not always demonstrable. In some infants the hemorrhage appears to arise from the engorged vessels of the choroid plexuses. More frequently, however, it appears to result from the rupture of one or more subependymal hemorrhages into the ventricular cavity. These subependymal hemorrhages are often located about the terminal vein between

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the caudate nucleus and the thalamus, although they also may be encountered at other sites. The subependymal hemorrhages in the stria terminalis thalami are located within cellular accumulations composed of small dark nuclei, variously referred to as medulloblasts[5] or simply as undifferentiated neuroectodermal elements.[6] These cellular aggregates are normal in the stria terminalis thalami and are especially prominent in premature infants.

TABLE I. LESIONS IN THE CENTRAL NERVOUS SYSTEM RESPONSIBLE FOR DEATH AMONG 100 INFANTS DYING DURING THE NEONATAL PERIOD

CAUSE OF DEATH	NUMBER OF CASES
Intraventricular hemorrhage	11
Kernicterus	5
Congenital malformations	4
Intracranial trauma	4
Thrombosis of dural sinuses	2
Leptomeningitis	2
Infarction of brain, extensive	1
Subarachnoid hemorrhage, extensive	1
Total	30

TABLE II. LESIONS IN THE CENTRAL NERVOUS SYSTEM CONTRIBUTING TO THE NEONATAL DEATH OF SEVENTY INFANTS*

LESION	NUMBER OF CASES
Intraventricular hemorrhage	4
Syphilitic meningitis	4
Kernicterus	3
Focal encephalomalacia	3
Dural tears	2
Subdural hemorrhage	1
Total	17

**Note:* Patients in whom the primary cause of death was thought to be a lesion in the central nervous system are excluded from this table.

They represent a normal developmental process and undoubtedly contribute to the formation of the striatal and thalamic masses. Hicks[7] has demonstrated that the necrosis of brain tissue induced in fetal rats by irradiation affects "principally the periventricular masses of germinal cells and neuroblasts which are forming the striatal and thalamic masses during the latter two weeks of gestation." Those animals exposed to irradiation in utero and subsequently studied from a few days to three weeks after birth revealed severe malformations of the brain. These malformations included almost complete absence of the corpus callosum and incomplete formation of the striatum. Wolf[8] has suggested that other deleterious factors acting at an equivalent stage of the development of the human nervous system might selectively injure the basal ganglia. It would seem that the subependymal hemorrhages occurring in premature infants might well represent such a deleterious factor. Such hemorrhages are not always accompanied by intraventricular hemorrhage. The presence of old blood pigment in the stria terminalis thalami of older infants dying of other causes tends to substantiate the view that these hemorrhages per se are not lethal lesions. What part they may play in the subsequent development of cerebral palsy remains unsolved.

Inflammatory lesions occurring during intrauterine life may lead to severe defects in the central nervous system. Toxoplasmosis and congenital syphilis are well-recognized intrauterine infections which may lead to severe neurological disorders. Bacterial leptomeningitis may occur during the neonatal period with few if any symptoms referable to the central nervous system. Recovery from the acute infectious process may result in permanent sequelae such as hydrocephalus, with resultant neurological manifestations in later infancy or childhood. Recent reports of the occurrence of subdural effusions in a considerable number of infants suffering from bacterial meningitis[9, 10] suggest the possibility that

such effusions might lead to permanent cerebral damage.

Apparently mild maternal infections may be related to severe congenital malformations in the offspring, as evidenced by the occurrence of congenital defects in the infants of mothers who suffered from rubella in early pregnancy.[11, 12] However, the manner in which maternal rubella causes congenital malformations is not clear. Experimental studies in lower animals indicate that a variety of deleterious agents applied to pregnant animals are capable of producing congenital malformations in the offspring.[13] Many of these agents probably play no role in the development of congenital malformations in man. Nevertheless, irradiation of pregnant animals may produce congenital malformations in the offspring of a variety of species[7, 13] including man.[14, 15, 16]

At the present time little is known concerning the relative importance of abnormal intrauterine environment and of defective germ plasm as a cause of spontaneous congenital malformations. Further knowledge concerning the fundamental nature of congenital defects is essential to an understanding of one cause of cerebral palsy.

Although kernicterus is commonly considered to occur only in association with erythroblastosis fetalis, there is evidence to indicate that similar findings may occur in nonerythroblastotic infants.[17, 18] Attempts to produce kernicterus by simple injection of bilirubin into the circulation of experimental animals have been unsuccessful, but pigment has been deposited in the brain substance when this has been injured, as by exposure to roentgen rays.[19] The evidence to date certainly suggests that the pigmentation of the brain in kernicterus is secondary to cerebral damage, but the cause of such cerebral damage is not established. Anoxia,[20] hepatic injury,[21] and direct injury of fetal cerebral tissue by maternal antibody[22] have been suggested as causative factors, but their role in the production of cerebral damage remains unproved.

If the pigmentation of the brain associated with kernicterus is actually secondary to underlying cerebral damage, it would seem possible that such damage might occur at times without associated pigmentation. There is some evidence to indicate that the clinical pattern of kernicterus occasionally may occur in the absence of pigmentation of the brain.[23] However, the histopathologic alterations in the brain of infants dying during the acute phase of kernicterus are so minor or nonspecific that an unequivocal diagnosis cannot be made in the absence of grossly demonstrable pigmentation. Better recognition of the clinical behavior of infants suffering from kernicterus, correlated with more careful study of the brains of infants who die after exhibiting such a clinical pattern, might lead to better understanding of an already accepted cause of cerebral palsy.

The role of intracranial trauma as a cause of cerebral palsy has received great emphasis in the past. Although trauma sustained at the time of delivery undoubtedly still accounts for an appreciable number of patients with cerebral palsy, its relative importance has probably decreased with improvements in the management of pregnant women. Nevertheless, two aspects of intracranial trauma occurring during delivery appear worthy of comment. First, considerable damage

to the brain may occur in the absence of large intracerebral lesions. We have recently observed two newborn infants who died as a result of intracranial trauma, manifested by tears of the dural septa and subdural hemorrhage. Although macroscopic lacerations or hemorrhages were not visible within the substance of the brain, histologic examination of the lungs revealed emboli of cerebral tissue in multiple smaller branches of the pulmonary artery. These emboli, which must have arisen from small lacerations in the brain, are indicative of the severity of cerebral damage which may occur in the absence of apparently significant macroscopic alterations in the brain.

Second, severe intracranial damage may occur during an apparently nontraumatic delivery. Tentorial tears may occur in infants delivered by cesarean section. We have observed huge bilateral tentorial tears, subdural hemorrhage, extradural hematoma, and a fracture of the left parietal bone in a premature infant whose delivery was apparently easy and uneventful; the presentation was vertex, outlet forceps were applied to the head, but no external evidences of trauma were visible at the time of autopsy.

Clinical or pathologic differentiation between traumatic intracranial hemorrhages and those secondary to anoxia is not always possible. Intracerebral damage secondary to anoxia, however, may occur without extensive intracranial hemorrhage. Although the newborn animal can withstand oxygen lack for longer periods than can the adult,[24] there is clinical and experimental evidence to indicate that periods of intrauterine anoxia which are not immediately lethal may lead to permanent cerebral damage[25, 26, 27, 28] Venous stasis, petechiae, and direct injury of neurones by anoxia all contribute to cerebral damage. Ultimately the affected areas may reveal disappearance of neurones, gliosis, and encephalomalacia. Since these same pathologic findings may be produced by a variety of agents, a careful clinical history is an essential part of any attempt to determine the responsible agent. Better recognition of the dangers of fetal anoxia and of the factors responsible for such anoxia should enhance our knowledge of the pathogenesis of cerebral palsy.

SUMMARY

Intracranial lesions are an important cause of neonatal death. Similar but possibly less severe lesions occur in the central nervous system of a significant number of infants dying during the neonatal period of other causes. The possible role of such lesions in the development of neurological disorders in later life is briefly discussed. Better understanding of the frequency and of the types of cerebral lesions found in newborn infants should contribute to our knowledge of the pathogenesis of cerebral palsy.

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MALFORMATIONS OF THE BRAIN—A NEGLECTED SOURCE OF BASIC KNOWLEDGE ON THE DEVELOPMENT OF CEREBRAL STRUCTURE AND FUNCTIONS

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THE ever-changing patterns of the neuronal assemblies in the brain epitomize the evaluation of the human organism as a biological action system. These patterns constantly sum and subsum the *phenogenic*, as well as the *ontogenic* and the *phylogenic*, history of the individual. All past experience is impressed upon living brain in the form of these patterns, somewhat in the manner of a palimpsest of neuronal assemblies in which upon the chronicle of the universal life experience common to all animals, the record of the specifically human life experience is inscribed, and one may reasonably assume that upon this record, which is common to all human beings, the history of each one of us is written, like a diary of intimately personal life experience, in the constantly changing configurations of the synaptic hookups of the cerebral cortex.

The decoding of this palimpsest is admittedly a formidable task. Yet it is not impenetrable. With suitable methods and dedicated patience one can unscramble, as it were, the meaning of the story told by the layer upon layer of reticulate, nucleate, and laminate neuronal assemblies of the neuroaxis.

Conel's work on the postnatal development of the cerebral cortex,[1] growing monumental in the four volumes already published and the fifth in preparation, provides the normative base line, a frame of reference for the study of abnormal development of the cerebral cortex. It affords access to a new area of research: *developmental pathoarchitectonics.*

The malformations of the cerebral mantle are, by and large, eminently suitable material for this area of research. One deals here with arrests of differentiation of the architectonic fields at different stages of development. The arrest is never uniform and so in the same specimen one may observe the whole spectrum of the organization of the cortical plate, from the rudimentary neuropil barely laid down to the fully differentiated, mature, six-layered cortex.

The agenesis of the cerebral mantle is often highly selective. Specific areas may fail to develop, while others reach a fairly high degree of differentiation. There is an order in this selectivity. In the areas of agenesis a cleft is usually formed.[2] The cleft may be a shallow pit or it may extend through the entire wall of the brain to the ependyma. Whatever their depth, the clefts are oriented in the axis of the primary fissures of the brain and so Rolandic, Sylvian, orbital, or cingulate clefts may occur. They may involve more or less wide areas of the brain. Thus, the entire pre-Rolandic mantle may fail, including the motor cortex, while the post-Rolandic mantle may be spared, or the Rolandic zone may alone develop, while the cerebral mantle

anterior and posterior to the Rolandic zone may be lacking.[3] Such malformations reveal principles of organization of the projection systems which are not discoverable by the method of experimental or surgical ablations. Neurotheratology should be an important complement to experimental and clinical neurology.

The malformations of the brain usually referred to as "monstrosities" reveal the intrinsic beauty of the experiments of nature which it is not as yet possible to reproduce by design in a laboratory. The "monstrosities," after having aroused an awed curiosity, are usually discarded as irrelevant autopsy material or, at best, stored in the museum jar for bemused contemplation. They should be studied as an extremely rewarding source of knowledge and understanding of the structure and function of the nervous system. Their study requires a specially organized and equipped laboratory, an effective method, and a clear realization of what information one may ask from such material. I am convinced that this area of research is highly pertinent to the problems of cerebral palsy, mental deficiency, epilepsy, and even of many less conspicuous handicaps of development and performance in children. This is a neglected field of inquiry.

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UNMET NEEDS IN CEREBRAL PALSY—IMPORTANT DIRECTIONS OF RESEARCH

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THE lesions in the central nervous system which are responsible for the complex of symptoms commonly called cerebral palsy are in the majority of cases not of a progressive nature. The victim afflicted with cerebral palsy suffers from a rather stationary neurological deficit. The attention of the physician is necessarily focused on palliative treatment. Treatment of cerebral palsy is confined very largely to physiotherapy, corrective surgery, and to methods of rehabilitation. At present, pharmacotherapy plays an insignificant role. Unquestionably, there is a very definite and urgent need for more effective drugs in the treatment of cerebral palsy. Having thus stated *one* of the "*unmet needs*" in this field, we may proceed to discuss briefly the direction of the research efforts in meeting this challenge.

It is the task of the pharmacologist to study the *site* and *mode* of action of therapeutic agents under experimental conditions and in the patient. What ways and means are available to search for more effective drugs, to investigate drugs acting in the central nervous system, and, possibly, even to design new drugs for the specific purpose of combating the hyperkinesia of cerebral palsy?

In localizing the *site* of action of a drug the pharmacologist is greatly aided by the recent advances in the recognition of better defined patterns of functional organization of the central nervous system. These concepts have developed as a result of the introduction of more exact electronic instrumentation. The functional patterns and their underlying anatomical systems have been studied intensively during recent years throughout the different levels of the cerebrospinal axis.

At the spinal level it is possible to separate the monosynaptic and polysynaptic components of several reflex ares, including the knee jerk and segmental reflexes. Thus, drug action on either of these systems can be detected. A whole new series of drugs is in fact known which in appropriate doses will depress interneurons, thereby abolishing polysynaptic responses while sparing the monosynaptic reflex arc.

Various methods of producing spasticity in experimental animals are available. Such animals manifesting increased interneuronal activity may be employed to demonstrate the effectiveness of drugs in selectively depressing interneurons, thus providing a rationale for clinical trials of such drugs.

Recently Magoun has discovered diffuse brain stem centers in the reticular formation which exert facilitatory and inhibitory effects on spinal cord reflexes. These relations offer means of studying drugs which act on the brain stem and the interneurons of the spinal cord. By recording the electromyograms of animals following decerebration, the effect of drugs on the result-

ing extensor tonus can be ascertained. Such experiments yield information as to the site of drug action by eliminating influences from higher levels. If a given drug exerts no spinal cord effects but the decerebrate rigidity is affected, then the site of action can be deduced to be in the brain stem or cerebellum.

Following operative lesions in the midbrain reticular formation, monkeys manifest a tremor at rest which in many aspects mimics that of Parkinson's syndrome. Dr. Mettler has placed lesions in monkeys and extensively investigated those which caused choreoid hyperkinesia, a preparation well suited for studying specific drug effects. By recording changes in action potentials of nuclear structures in the brain stem, it may be possible to localize drug action even more accurately.

The site of action of useful antispastic agents in affecting the cerebral cortex is of importance since depression of the sensorium should be absent or at least minimal. Cortical changes can be demonstrated in the electroencephalogram. High frequency waves characteristic of the waking state are thought to originate in large part from the ascending projections of the brain stem reticular formation. Sleep, both spontaneous and induced by certain hypnotics, or separation of the forebrain from the activating center by mesencephalic section is accompanied by large amplitude, synchronized low frequency spindle bursts in the electroencephalograph. It is thus possible to differentiate drug action on the reticular formation from that on the corticothalamic complex. While sleep abolishes the hyperkinesia of most cerebral palsy patients and also the tremor of Parkinsonian patients, the ideal in pharmacotherapy is to inhibit the abnormal movements and yet retain the full conscious faculties of the patient.

Parallel to the problem of determining the site of action is that of establishing the *mode* of action of a drug at a cellular level. The mode of action by which drugs alter cell metabolism is known at present for only a few drugs. The information about drug action on brain cells is just beginning to emerge. However, biochemists have been making great strides in elucidating the metabolism of brain cells. Present concepts of brain metabolism rest upon the fact that carbohydrate is essentially the sole source of energy. Energy transformation may be regarded as proceeding in steps. The first phase comprises the production of energy by oxidation of glucose catalyzed by a complex system of enzymes. In the second step the energy thus liberated is stored by the formation of high energy phosphate bonds such as those of adenosine triphosphate, which may be regarded as the immediate source of energy for cell function. The mechanism of transferring the energy obtained from oxidation to its storehouse, adenosine triphosphate, is likewise an enzymatic one.

A third phase is represented by the utilization of expenditure of energy from the breakdown of adenosine triphosphate. This phase may be of particular importance in the synthesis of acetylcholine.

Recent concepts of energy transfer in the brain open new vistas for the mode of action of drugs. The most vulnerable sites for drug action may be found in the enzymatic processes governing oxidation, in phosphorylation or formation of high energy phosphate bonds, or finally in the enzymatic

breakdown into metabolites associated with specific cell function.

Experiments demonstrating drug action on specific phases of the energy cycle are within our reach and will undoubtedly make significant contributions to our knowledge in the near future. Still, there remains the gap between energy and function. Exactly how and in which form is the energy connected with function?

It may be well to recall at this time that our concepts of mediation of impulses at synapses in the central nervous system are still deficient.

Since Loewi's classical experiment demonstrating humoral transmission in the frog heart, transmission of nerve impulses in the autonomic system has been extensively studied. It is generally agreed that acetylcholine is the chemical mediator in autonomic ganglia and at parasympathetic effector synapses. Its effect can be blocked by atropine and potentiated by anticholinesterases. We also know that impulses at sympathetic effector synapses are transmitted by an epinephrine-like compound and that certain sympathetic effects can be modified by adrenergic blocking agents. At the neuromuscular junction in skeletal muscle acetylcholine has been proposed as the chemical mediator and the specific blocking effect of curarizing agents at this site is well known. Also the antagonism of curare by anticholinesterase drugs and by acetylcholine has been studied extensively and most of this information supports the chemical mediator theory.

In contrast, the mechanism of central synaptic transmission is the subject of great controversy. The possibility exists that central synaptic transmission occurs by similar but more complex processes than those which mediate autonomic and peripheral impulses. Some progress has been made through reasoning by analogy from peripheral reactions, but definite information is lacking. There are several reasons for this. It is extremely difficult to isolate and study single synapses in the central nervous system because of the anatomical arrangement of the large masses involved. Thus structural complexity interferes with both electrical and pharmacological investigation of the nature of synaptic reactions.

My brief and arbitrary sketch presented some of the ways and means at our disposal—and some of the obstacles and gaps yet to overcome—in our approach to effective pharmacotherapy of cerebral palsy. Progress in the development of rational and effective pharmacotherapy for cerebral palsy can be made only by the concerted efforts of many researchers in neuroanatomy and neuropathology, in biochemistry, and in neurophysiology and neuropharmacology. And all of them need the cooperation of the clinician. The concepts, the tools and the instrumentation with which we can meet this challenge have been contributed by all the different branches mentioned. The process of cross-fertilization between these research fields will be most important in applying present knowledge and new techniques successfully to the task.

UNMET NEEDS IN CEREBRAL PALSY

Follow-up Study of Children With Cerebral Palsy

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SO FAR AS I am aware, no longitudinal studies of the evolution of cerebral palsy, in terms of progression through infancy, childhood, adolescence, and into adulthood, exist. We very much need such a study, and I would like to outline the basis required for, and some possible results of, such a follow-up, and lastly to suggest that an undertaking such as this will attract and lead to subsidiary investigation.

The basis requisite for investigations of this sort is a large number of patients studied over a period of many years by the most appropriate methods possible. At the Children's Hospital in Boston we have been interested in cerebral palsy in an intensive way for over twenty-five years, and twenty-two years ago a neurological ward was added to our plant by the kindness of the Rosenwald Foundation, and a staff was subsidized by the Commonwealth Fund to inaugurate the study of neurological hospital patients, a financial burden gradually assumed by the Children's Medical Center and Harvard Medical School.

During these years approximately 7,000 patients have been admitted to our ward for study and treatment, and of these it is estimated that 1,500 or 2,000 were examples of cerebral palsy in one form or another. As we became more proficient in assessing cerebral palsy on an out-patient or office basis, we admitted relatively fewer patients, and our hospital studied cases must, at present, contain a high percentage of adolescent and young adult individuals.

As our experience grew, we developed a more and more anatomical, psychological, and physiological approach to the disease. Dr. Crothers' interest in the anatomical side is exemplified by large numbers of pneumoencephalograms done and studied under his direction. He pointed out the changes in size of the ventricles which accompanied cerebral damage of varying degree, and the changes in position of the ventricles incident to unequal injury to the hemispheres early in the period of rapid growth.

Dr. Elizabeth Lord was our first psychologist, and her studies into the psychopathology of cerebral palsy still remain fundamental to the disease. She pointed out that in cerebral palsy the correlation usually obtained between I.Q. and educability did not hold, and that a much more searching appraisal was required to describe the learning capacity following cerebral injury or maldevelopment. In brief, she explored defects of attention, of perceptuo-motor capacity, of abstract synthetic capacity, and found in these fields a fruitful explanation of educational failure. The younger children showing such difficulties she classed as potential educational failure.

I became interested in the postural aspects of cerebral palsy, and after

study of the German literature on the subject, have been interested in the meaning of tonic neck reflexes and neck righting reflexes. Normally present in early infancy, such reflexes should be suppressed by the development of more adult postural patterns in the forebrain by the end of the first year. The persistence of such patterns bespeaks a degree of decerebration inconsistent with well-controlled voluntary motor activity. The emotional aspects of cerebral palsy have interested us all, and at your meeting in New York early this year, Dr. Crothers detailed for you his concept of the delayed or inhibited adolescent rebellion common in this disease. Dr. Meyer, who has taken Dr. Lord's place as psychologist, has amplified the latter's work and has pointed to its influence in emotional development. In addition, she has lately described very fully the effects of poverty of experience on personality development in cerebral palsy. While such observations were not made on the older individuals in our material, it is obvious that her thesis is a general one and can be assumed to have been operative in the more severely handicapped children.

Physiotherapy seemed to us to be the probable answer to cerebral palsy when we began caring for the patients, and we have had extensive experience with it in all types of cases. Braces, casts, and other apparatus have been used in some individuals, and orthopedic operations in a moderate number. Neurosurgical operations have been tried in a few individuals, either on the tracts or on the premotor cortex. Electroencephalographic studies have been made in the past nine or ten years with gradually increasing frequency, and it is possible that enough cases have been so studied as to allow of some assessment of the predictive value of the method.

The work of Magoun on "Inhibition and Facilitation of Muscle Tone," reported at your spring meeting, was not published when our case collection was made. It should be possible, with the help of the case histories and pneumoencephalographic studies that we have collected, to attempt an assessment of his ideas in relation to clinical cases. We all remember individuals with striking changes in muscle tone which seem to fit into his hypothesis, but so far no systematic appraisal of any large clinical material in such terms has appeared.

Our feeling is that no comparable group of cases exists, either from the point of view of age or completeness of preliminary study. With your help, Dr. Crothers is now undertaking a follow-up of as many cases as can be found. Since the study is needed, it is not possible to say what its results will be, but a few of its aims may be suggested. What are the long-term prognostic values of pneumoencephalography? Are persistent primitive postural patterns which persist in the second or third year ever developmentally suppressed? Are the psychological disabilities described by Dr. Lord as potential educational failure always permanent? What motor deficits have persisted and what psychological assets are required for a successful adolescent rebellion? What influence has physiotherapy appeared to have on motor defects of various types? How many of our children are now gainfully employed, and in what employment have they been able to maintain themselves? How many

can be a help to their homes? How many are totally dependent? What types of emotional stress are common and what factor in their genesis can we describe?

We think we know the answer to some of these questions, but we have never had the leisure to pursue a systematic appraisal of our results. The importance of such an appraisal to the understanding of cerebral palsy is obvious, but, in addition, if carried out by Dr. Crothers, who knew and remembers many of the parents well, its value will be increased. You have already given him a mandate to go ahead and he is in the organization stage of the investigation. We are hoping for funds from the U. S. Public Health Service to supplement the gift already made for this purpose, for such a study will require not only a salary for the chief investigator but should also envisage expenditures for social service and secretarial help, psychological appraisal, hospitalization, electroencephalography, and other medical help. Finally, such a study always attracts students in related fields. We already have a fellow from Queens Square who has taken on as a project a study of the behavior aspects of acquired hemiplegia in infancy and early childhood. He has already found records of over 200 such cases, and arrangements are in progress for contacting and studying as many as possible of these cases. Since his stay will be only a few months, it will be impossible to complete the entire 200. He is interested in the problems because of the frequent use of hemispherectomy in England as therapy for behavior problems arising in such cases.

Such then are our plans and hopes. It will necessarily be some time before we can present much in the way of results. I rather foresee that those who have done well will be hard to find, and that the more thorough we can be the more representative our results.

Medical Progress

HEALTH SUPERVISION OF INFANTS AND CHILDREN

A Statement for the Midcentury White House Conference on Children and Youth*

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ONE of the fundamental objectives of a democratic society is the realization of the greatest potentialities of each individual in order that the responsibilities of mature citizenship may most effectively be met. Toward the achievement of this end, the Midcentury White House Conference centered its activities about "how we can develop in children the mental, emotional, and spiritual qualities essential for individual happiness and responsible citizenship, and what physical, economic, and social conditions are deemed necessary to this development."

Optimal health for every individual is fundamental to the ultimate realization of these objectives and is generally regarded as an inalienable right of all sections of the population. The World Health Organization has suggested that optimal health be interpreted broadly as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." In this sense, the extension of preventive health services, which was a major health objective of the first half of the twentieth century, becomes only one feature of a more positive health program for infants and children which assures each individual complete health supervision progressively from prenatal life through adolescence. In the latter half of the twentieth century, the implementation of this program should become a reality.

The health record of infants and children during the past several decades as measured by morbidity and mortality figures has been remarkably improved. Advances in the fields of bacteriology, epidemiology, immunology, public health, chemotherapy, metabolism, and nutrition have made great contributions to the reduction of infant and childhood mortality from the common infectious, metabolic, and nutritional disorders. In the face of these advances, the morbidity and mortality from accidents, neoplasms, and emotional disorders become more prominent as health hazards. Thus, health supervision must ever be dynamic and alert to shifting emphases which challenge present practices and demand new approaches. Certainly, the control of these disorders cannot be achieved by broad application of single techniques such as immunization. Rather, the character of health

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problems today demands careful, close, skilled, individual supervision as a basis for a constructive program.

The greatest challenge to current practices in infant and child care in the United States today is the increasing recognition of the magnitude of the problem of mental ill health in our population. Certainly, the facts that one million children attending public schools today will spend some part of their lives as patients in mental hospitals, that more than half the patients in hospitals on any given day—some 600,000—are mental patients, that two million men were either rejected or discharged by the Armed Services because of neuropsychiatric disorders during the military mobilization of World War II, all portend serious consequences to our culture unless this trend is minimized. The additional burden of subclinical emotional disorders, which to some extent handicap a large proportion of our population, is immeasurable and adds greatly to the dissipation of human resources. Since emotional disorders, regardless of the age at which they are manifest, reflect the background of the individual's total development, any measure designed to minimize their incidence must be projected into the early care of infants and children.

In the light of this background, the health supervision of infants and children must be re-evaluated and a constructive program and practices projected. Fundamental to a really effective program is continuity of care by well-trained professional personnel which provides an opportunity to observe the longitudinal development of the child. Such continuity facilitates effective guidance which is dynamic while providing an opportunity to detect incipient disorders—physical or emotional—promptly in order to minimize their hazards. A desirable by-product of a program of this character will inevitably be the development of more information on the early manifestations of all threats to the health of the individual.

Because he encompasses the disciplines of medicine, human development, and to some extent social work, psychology, education and related fields touching upon child care, the physician is destined to play the central role in the implementation of any program of health supervision of infants and children. This necessitates a change in pediatric education, which must adapt itself from teaching centered largely about the sick child to that of total health of children, with an emphasis on the physician's role in health supervision. Evidence that pediatric education is increasingly adopting this emphasis is evident from the improved orientation of recent medical graduates. That medical education has not provided this orientation in the past was demonstrated by the American Academy of Pediatric Survey of Child Health Services and Pediatric Education which found that of the general physicians who provide 75 per cent of the medical supervision of infants and children, 50 per cent have had less than one month's training, beyond medical student days, in the care of children. Since postgraduate training provides the most practical and informative training in child care, this represents a significant defect indeed. Although the general physician spends approximately 30 per cent of his time caring for children, 66 per cent of this time is devoted to caring for sick children as con-

trasted to the pediatrician who spends only 43 per cent of his time caring for sick children and 54 per cent of his time caring for well children. This is a reflection of the difference in education and emphasis in postgraduate training. Certainly, a concomitant of changing pediatric education in teaching centers must be a comprehensive program of postgraduate education designed to reach all physicians providing care to children.

There seems to be general agreement that every infant and child in the United States should be receiving continuous health supervision. That such supervision, even with present qualitative defects, is uneven in distribution and lacking in continuity, for significant numbers of the young population, was demonstrated in the Academy study. A realistic objective is the improvement of these services quantitatively and qualitatively to make them adequately available for all.

The precise pattern which total health supervision will follow cannot be entirely stated at present and it is unlikely that any single pattern will ever apply to all situations. Certain changes over what has constituted "well-baby or well-child" supervision are highly desirable, however. Particularly the current concept of the well-baby clinic, which cares for the infant only when he is well and refers him elsewhere during illnesses, or which does not provide an opportunity for home visits and an evaluation of the entire family constellation, is not fulfilling its function well. Ultimately, these clinics—whether conducted by voluntary or public agencies—must become the proving ground for developing broad programs of child care which will include supervision which is complete and continuous. Certainly, these clinics must become the training centers for physicians and all professional workers interested in the care of children in order that they may learn to function effectively together and to know how each discipline may contribute to total care.

These clinic activities which provide service as well as demonstration programs should not in any way be interpreted as a threat to the practicing physician. The relative lack of availability of all professional personnel, the problems of training adequate numbers for some years to come, and the general pattern of distribution of medical care in the United States indicate that care rendered by the practicing physician will be the fundamental unit in health supervision. This emphasizes all the more the importance of his training in child care, of focusing his interest on child-rearing practices, of providing him with "guidance" capacities to assist in attaining optimal health for every family. The physician, by virtue of the fact that he is the one person qualified to see the child during health as well as illness, and in the home as well as in the office or clinic, is ideally situated to fulfill this role. In this process, even when he is not working in a clinic setting, ways must be found to make more readily available to him the services of the public health nurse, nutritionist, social worker, occupational therapist, physical therapist, dentist, psychologist, and all necessary consulting services. The fact that families may find it possible to pay for a portion of these services should not deprive them of services available to

those considered indigent. In our programs for handicapped children, we have gone a long way toward a realization of these objectives. Our children without crippling defects do not deserve less.

It must be recognized that effective health supervision, designed to maintain optimal health of the individual, must be provided individually. The techniques of preventive medicine which may be applied en masse do not provide an opportunity to consider the problems of the individual child and parents adequately. This is particularly true in the sphere of emotional problems. Even educational activities for parents must be undertaken with considerable care, always with provisions for discussion of individual problems. By these standards, the busy clinics and practitioners' offices in which children, parents, and professional staff alike are harassed by the pressures of time are distinctly unsatisfactory. Hence, conventional yardsticks for determining standards of adequate professional services no longer apply. It is obvious that increased numbers of all professional personnel caring for children will be necessary. Pilot studies to determine personnel requirements and the facilities for training should have a high priority at this time.

With these general comments as background, we may proceed to a consideration of practices designed to provide health supervision for infants and children. For purposes of presentation, these will be presented with reference to age periods. In fact, however, there is no sharp delineation of practices related to specific ages; rather a longitudinal blending of these practices serves the best interests of developmental supervision of infants and children.

Practices in the Health Supervision of Infants and Children

PRENATAL

Introduction.—The health supervision of the infant optimally has its origin in the prenatal period. During this period, preparation of the entire family for child rearing should take place. It should eventually be our goal to develop educational practices and guidance of the emotional development of children which will, as they approach maturity, prepare them more effectively for parenthood. There is general agreement among many professional people, that an emphasis in our culture has developed which to some extent relegates childbearing and child rearing to an inferior role. Obviously, a shift toward a more wholesome emphasis can occur only after a realization of the long-term impact of this trend by leaders in our national life and by all professional people and groups concerned with human relations in the broadest sense. The responsibility for attainment of a more wholesome philosophy concerning child rearing is not the vested interest of any single professional group; it is a responsibility of our entire people. The White House Conference emphasized this responsibility and made suggestions for remedial measures. In this light, specific problems related to the prenatal period may be discussed.

Emotional Problems of Parenthood.—Regardless of background, all prospective parents face problems concerning personal adaptation to a new relationship. This is particularly true of

prospective parents anticipating the birth of a first baby. Adequate facilities to assist each family, whether the problems require counselling service or extensive psychotherapy, should become generally available. The precise pattern for providing such facilities is not entirely clear, but adequate demonstration programs exploring the feasibility of such services have been developed to point the way toward a realistic implementation of desirable programs generally.

During this phase of development, any program must intimately involve the obstetrician and obstetric services. Since obstetricians in private practice provide a large percentage of the obstetric care of the nation, it is important that obstetric training programs increasingly encompass the teaching of emotional problems relating to childbearing. The pressures of time on the practitioner have thus far tended to cause a considerable neglect of these problems. The pattern of obstetric practice has emphasized physical care in pregnancy predominantly. It is unlikely that we can at any time in the near future train adequate numbers of physicians who practice obstetrics to encompass all of these functions individually.

Because of these practical problems relating to the obstetric physician's care for the emotional problems of pregnancy, it seems likely that centers staffed by properly trained personnel in various of the health professions will be developed. These could be utilized by the practicing physician to supplement his obstetric care and should also be adequate to render complete obstetric service to those requiring them. Programs, such as the Cornelian Corner in Detroit, the Rochester Child Health Study Project, and various of the prenatal counselling services which have developed in relationship to rooming-in programs for newborn infants, have demonstrated the effectiveness of work during the prenatal period.

In projected prenatal centers, the minimum requirements must be competent obstetric, pediatric, and psychiatric consultants, in addition to nutritionists, social workers, public health, obstetric and pediatric nurses, and health educators. Particular care must be exercised in the selection of personnel to recruit individuals who have a wholesome sensitivity to parental problems combined with an appropriate perspective of the contribution of each discipline represented on the professional team to the common goal. An immature, inexperienced professional worker may throw a potentially effective program into disrepute by attempting to prove that his or her profession has the major contribution to make to the family. The selection of personnel for training purposes on the basis of individual adaptability is of primary importance.

Whether these programs develop under private or public auspices should be determined by community needs. It is likely that for many years to come, we will observe their development under both. These services should be sufficiently available so that no family arrives at parenthood without an opportunity to resolve its problems relating to child rearing.

Because of their importance in prenatal, neonatal, and infant care, certain problems of special current interest in relationship to prenatal preparation will be touched upon. An adequate program of prenatal prepara-

tion should provide instruction in the physical care of infants. Also social services may be employed to assist with specific problems concerning the birth of the baby, whether these be cultural, economic, housing, legal, or otherwise. While this may to some extent be accomplished during the lying-in period, the time available is generally inadequate and the many anxieties harbored by parents regarding their capacity to care for an infant may be resolved effectively much earlier. Also, the father may be brought into the program advantageously at this time. His role, it has been demonstrated, should most effectively be in the direction of psychologic support to the mother as well as in assistance with the physical care of the infant.

During this period preparations may be understaken to form the basis for a rooming-in program. Rooming-in for the newborn infant is generally regarded to be a step forward in establishing a more wholesome relationship between the infant and parents. Again, the father has been intimately involved in these programs. It must be emphasized that the success of a rooming-in program is dependent upon the preparation of both parents and staff for it. If this preparation is inadequate, the program may fall into disrepute. The success of existing programs has hinged on this preparation period. Where inadequate preparation for rooming-in has been made, as occurred on one private obstetric service, less than 5 per cent of families availed themselves of this service.

Somewhat related to a rooming-in service are newer programs concerned with the emotional aspects of childbirth. Programs providing for "natural childbirth" and the exploration of obstetric anesthetic and analgesic agents of various types require continuing investigation to determine which may most advantageously be employed from the standpoint of emotional impact as well as maternal and infant morbidity and mortality. The basis for breast feeding of the infant may be developed at this time also.

Considerable investigation remains to be done in the area of psychosomatic problems of pregnancy which may have an important bearing on the development of infants and children. That vomiting in pregnancy may reflect significant emotional problems has been appreciated for some time. The relationship between toxemias of pregnancy and emotional problems merits further exploration. Closely related to these investigations must be provisions for adequate individual psychotherapy as indicated. Although much of the prenatal program can be undertaken in groups by classroom and discussion techniques, provision must always be made for individual discussion and guidance or therapy. This should be true for prospective fathers as well as mothers.

Physical Care.—It might perhaps seem unnecessary to discuss adequate physical care during pregnancy in relationship to health supervision. However, since disorders, such as toxemias of pregnancy, hemolytic disease of the newborn as a result of blood group incompatibilities between mother and infant, nutritional disorders, and maternal infections, may have serious consequences on the fetus and infant, adequate prophylactic care and prompt therapy are essential to a complete program. The assurance that physical care is completely ade-

quate relieves many potential parental anxieties in pregnancy. Regular obstetric visits with frequent measurements of weight and blood pressure, serologic tests for syphilis and blood groups and frequent urinalyses are basic to such supervision. The uneven geographic distribution of obstetric services is reflected in the variation in maternal and newborn morbidity and mortality in the various states. More adequate distribution of services would significantly lower nationwide maternal and infant morbidity and mortality rates.

Nutrition.—Studies have indicated that inadequate maternal nutrition during pregnancy is attended by hazards to the fetus. This has not been borne out entirely in studies of populations subjected to nutritional privation. Certainly enough evidence is now available to indicate that it is not sound to permit maternal undernutrition, since it is recognized that the fetus may receive nourishment at the expense of the maternal organism. Such undernutrition does not enhance the mother's capacity to care for her infant. Educational opportunities concerning nutrition for the entire family also may be advantageously undertaken at this time.

Prematurity and Postmaturity.—Because it is the greatest single cause of infant mortality at the present time, prematurity merits special consideration. Until recently, major emphasis has been placed on metabolic investigations of prematurity in order to reduce the mortality of premature infants. These efforts have had a desirable effect; further efforts to define more clearly the causes of death in premature infants will have a salutary effect. However, a more fundamental approach centers about reducing the incidence of prematurity. It is significant to observe that little is known concerning specific causes of prematurity. As such information develops, it will undoubtedly influence prenatal care significantly. Recently, prolongation of pregnancy (postmaturity) has also been demonstrated to be associated with increased hazard to the fetus and newborn infant. A better understanding of this problem is also awaited by clinicians.

INFANCY

Introduction.—The increasing acceptance of regular health supervision for infants is in distinct contrast to other age periods. This supervision, whether provided by an individual practitioner or an infant welfare clinic, has in general been concerned more with "preventive measures," such as feeding instructions and immunization rather than with total care. Attention to the emotional development of the infant has particularly been lacking; indeed, many programs of infant care have violated fundamental precepts of mental hygiene. The great limitations of time which provide no opportunity for parents to discuss problems concerning the development of the infant or child is a serious defect of present infant care. The relative lack of training and interest of physicians and other professional workers has also been a contributing factor. Serious consideration, both in the physician's office and in clinics, should be given to spacing visits less frequently, but for longer individual sessions until more adequate facilities become available. Physicians with more adequate training can employ even limited periods

more effectively. Continuity of care, previously emphasized, can also serve to facilitate acquisition of information and guidance which may be provided even within limited time. The utilization of social workers, nutritionists, and public health nurses should be available to the practicing physician as well as to the clinic physician as he finds it desirable to employ these professional services.

A forward-looking program of health supervision must reflect a practical application of a dynamic philosophy of growth. An appreciation of the developmental patterns of infants and children must become part of the professional equipment of every worker in this field. In the light of this philosophy, some specific practices of infant care will be considered.

Development.—Regular assessment of the physical, mental, emotional, and social progress of each infant is fundamental to adequate health supervision. While genetic factors play some role in determining growth and developmental patterns, it is now well accepted that these patterns are considerably influenced by postnatal factors. The interrelationships among these areas of growth become increasingly apparent; thus physical factors may exert profound influence on emotional growth and vice versa. Techniques for evaluating growth and development in all spheres must be refined, particularly in the assessment of mental, emotional, and social growth. The evaluation of physical growth by methods developed by various investigators is generally much more satisfactory. A valuable program for developmental supervision of infants which also provides for physical care has been presented by Aldrich and Hewitt.[1, 2]

Since the behavior of man is differentiated from lower animals largely because of the development of his central nervous system, detailed examination of neurological development is important. Detailed assessment early in life may provide the basis for a decision as to whether neurological disorders are congenital or acquired in origin. The possibility that parents will be provided a false sense of security concerning the developmental progress of their infants is minimized by adequate early examination.

Examination of the central nervous system in early life depends primarily on the observation of primitive reflex patterns and the orderly development from relatively mass movements to more complex and differentiated patterns of neuromuscular integration in a cephalocaudal direction. No observation of an infant or child is complete without an objective recording of neuromuscular activity from which progress may be judged. Thus sucking, rooting, and tonic neck reflex activities in the newborn infant are important observations. The timetable of the appearance of smiling, head control, oculomotor control, vocalization, sitting, creeping, standing, and walking, all have significance in developmental assessment. None of these criteria are of significance as isolated considerations; the pattern must be considered totally. Skill in interpretation of these patterns requires intensive training.

The orderly pattern of neuromuscular development has caused some individuals to regard this as an inevitable accompaniment of maturation which is not subject to influences other

than time. The classic studies of Spitz and others have amply demonstrated that failure to provide a stimulating environment in the form of loving, warm, human experiences will not only produce manifestations of neuromuscular retardation, but physical deterioration as well. Health supervision in this age period should, therefore, provide warm relationships, whether the infant is in the home, hospital, or an institution. The fact that developmental patterns are subject to influence may reflect the fact that neuronal projections are not fully developed at birth as Conel has demonstrated. Thus, use may exert considerable influence on physiologic and possibly even anatomic development of the central nervous system.

The susceptibility of the central nervous system of the young infant to external influences and its adaptability may perhaps provide some biologic explanation of the importance of the early emotional environment of the young infant. Psychiatrists have long been cognizant of the significant effects of this early period on future emotional development of the individual. Indeed, many emotional problems in children and adults may have their origins to some extent in rigid, impersonal care and emphasis on "training" in early life which medical practices tended to foster in recent decades. A wholesome trend is therefore emerging in infant care to provide for the individuality of each infant with full respect to his developmental patterns and the attitudes of parents.

Rooming-in programs have already been discussed as one aspect of a wholesome parent-infant relationship. Breast feeding—both to provide a species specific, biologically desirable food and to provide a close mother-child relationship—should be encouraged and become more widespread. In a period of transition, it is wise to caution against pressing mothers who are psychologically inadequately prepared to breast feed their infants into doing so, lest one defeat the desired objective. Greater anxiety and even hostility may develop under these circumstances.

In general, it is now agreed that it is desirable to encourage parents to exercise a more understanding, permissive attitude toward their infants and children than has heretofore prevailed in our culture. Understanding and respect, both from the standpoint of neuromuscular and cerebral performance, for developmental patterns should prevail. In the process of education of professional personnel and parents toward this point of view, enthusiasm has, on occasion, displaced reason with the result that an impression that parents play no positive role in the child's development has become prevalent. Disturbance in sleep habits during the latter part of the first year of life is an example of the end results of such misinterpretation. Rather, parents optimally are secure figures with individuality and wholesome spontaneity in their relationships with children. Certainly, satisfactory identification with parental figures does not develop unless parents can adequately provide stimulation for the growth of the child which does not exceed his capacities. Individual conferences providing an opportunity to discuss all parental problems relating to child rearing in a receptive, unhurried atmosphere is basic. No broad educational program can obviate the need for individual conferences.

With understanding attitudes, many specific problems of infant care are managed more appropriately by parents. This should parallel a program of "anticipatory guidance" in which parental anxieties are minimized by providing an explanation of forthcoming developmental patterns and problems. Thus, during the rapid weight gain and relatively great food intake of the first year, explanations anticipating periods of "physiologic anorexia" of the second year may be given. Bowel and bladder control and guidance to facilitate such control may avoid difficulties. These discussions provide excellent opportunities to learn of parental attitudes, to provide insight into the developmental processes of the child, and to encourage a reorientation toward bodily functions generally. As a result, parents may develop a better relationship with the child in such areas as sex education.

Since emotional problems in early life manifest themselves as disturbances of physiologic function frequently, such disorders as colic, vomiting, constipation, diarrhea, and irregular sleep patterns should cause the physician to assess the family relationships. In these disorders, a visit to the home may be particularly informative. Parental relationships may be observed more intimately; the role of siblings may be evaluated more fully. To support an adequate mother-infant relationship, it is increasingly clear that paternal support to the mother—even though it does not involve direct physical care to the infant—is of considerable value in maintaining a desirable relationship.

Feeding.—The advantages of breast feeding have been presented by the National Research Council Committee on Breast Feeding.[3] If artificial feeding is necessary, it is believed desirable to simulate the breast feeding situation as closely as possible. Parents should be provided adequate, practical instructions for the preparation and conduct of the feeding. That the nutritional requirements of infants can be met entirely and satisfactorily by artificial feedings is well established now.

Special feeding preparations which claim to simulate breast milk are not necessary in general. Except in rare instances, entirely satisfactory feedings may be obtained by simple variations and modifications of cow's milk with the addition of vitamins A, D, and C.

The tendency to introduce semisolid foods into the infant's diet earlier than the third month is unfortunately becoming more prevalent. No nutritional need for additional foods at this age has been adequately demonstrated. In addition, the introduction of spoon feeding at this early age is often beyond the neuromuscular capacity of the infant. Because of the significance of oral activities in infancy in emotional development, feeding techniques which are troublesome may have far-reaching consequences since they promote anxiety of parent and infant. For similar reasons, the weaning process should be undertaken gradually as the infant indicates readiness to give up breast or bottle feedings.

That infants have self-regulatory feeding patterns which are regular and rhythmic has been demonstrated by Aldrich and Hewitt.[4] In practice, respect for these patterns has worked out very well except in unusual instances in which a mother cannot ac-

cept the relative flexibility of the program.

Immunization.—The reduction in incidence of the acute infectious diseases should not permit a relaxation in the application of immunization procedures. In many areas, relatively few infants and children are being adequately immunized.

Recent evidence has proved rather conclusively, in contrast to previously held opinion, that the newborn infant is capable of manufacturing antibodies. Particularly because of the hazards of pertussis, immunization in the early portion of the first year is desirable. All infants should be immunized to pertussis, diphtheria, tetanus, and smallpox as a minimum. If the initial immunization is in the early months of life, a booster of triple antigen (diphtheria, tetanus, and pertussis) should be administered at the end of the first year. Immunity should be maintained by similar booster injections during the preschool, school, and adolescent years. Precise practices are subject to the preferences of individual clinicians; as a general rule, however, frequent small booster doses are more effective in maintaining immunity than are less frequent but larger doses.

In some regions, additional immunizations against typhoid fever and typhus may be desirable. For families traveling into areas in which yellow fever and cholera are endemic, immunization against these diseases should be undertaken.

Recently, the possible predisposure effects of injections to poliomyelitis has caused health departments to recommend postponing immunization during the poliomyelitis season. Until contrary evidence is presented, this is probably a wise policy.

PRESCHOOL

Introduction.—The preschool years are significant in the development of personality and social patterns. In addition, infectious disorders, particularly those of the upper respiratory tract, occur frequently. The latter offer an opportunity to observe the child in the home setting if continuity of care is assured.

Emotional Development. — Because these years are characterized by the establishment of habit patterns and interpersonal relationships which are the essential factors in shaping personality development, regular health supervision during this period should significantly focus on the emotional development of the child.

Developments in our culture have not been conducive to providing wholesome environment for preschool children. The general demand for conforming, mature behavior from young children has been one manifestation of this. The motor activity characteristic of children in this age period has been hampered by the trend toward urbanization with more crowded living conditions. Potential harm results from thwarting this energy outlet. By contrast, the child in a rural environment, while perhaps having adequate outlets for motor activities, often is subject to social isolation at a time when contacts with other children may be important in personality development.

The individual physician and the entire professional personnel staffing clinics should be alert to these problems in order to facilitate a good environment. The role of an adequately

staffed nursery school serving as a guidance center in close collaboration with health personnel, clinics, and individual physicians in both rural and urban areas, deserves much broader exploration in this country. The opportunity to observe the child at play, his relationships to his contemporaries, and staff discussions of developmental progress and problems which are appropriately presented to parents in turn are guidance opportunities which can facilitate wholesome personality development and detect disorders at an early time. The study of adult personality disorders has demonstrated repeatedly the origin of many emotional disturbances in this age period which, by appropriate guidance, could have been avoided. Educational activities concerning child development for parents and ample opportunities for unhurried discussion of individual problems should be central features of health supervision at this age period. The nursery school can offer these opportunities in part.

Physical.—Regular assessment of physical growth and development is a good index of the general health of the preschool child. Medical supervision during acute infectious diseases to provide prophylactic and therapeutic measures should be readily available. The observation of the child and parents during the minor and major illnesses which occur during this age period provide an unusual opportunity to observe the dynamics of interpersonal relationships in the family. Parental anxieties may be highlighted; overprotective tendencies may be noted; feelings of guilt about previous relationships with the child may become obvious. Thus, adequate care for the medical problem is only one feature of medical care. Particularly important, especially during prolonged illness, is the avoidance of overprotection and infantilization which may develop, although some regression is to be anticipated. The full interpretation of these manifestations may require psychiatric consultation in individual instances.

SCHOOL YEARS

Introduction.—The school years are generally considered to be the most healthful period of childhood. This reflects itself in the almost total absence of organized health supervision for children of this age group with a few outstanding geographic exceptions. While health as measured in terms of morbidity and mortality may be relatively good, few children attain their greatest potentialities during this period. Since this is a period of active learning, health supervision should be directed at making the child's learning experience as effective as possible. This requires a somewhat different emphasis in the physical examination and a more adequate concentration on the emotional problems relating to the school situation and the age period. Again, individual health supervision which is continuous from birth would be most advantageous. The orientation toward school health in this light would shift from a concern with health examinations predominantly (since these would be appropriately performed by the physician or agency providing the child's total care) to one of introducing effective, progressive health education in school curricula, medical consultation in physical education programs, supervision over environmental and sanitary facilities (which from a health point of view

have been largely neglected), and the conduct of in-service training program for all school personnel which would offer orientation in child development to teachers and administrators. The latter is largely lacking in our educational programs. Guidance and counselling facilities for faculty and students should be an integral part of this program. During a period of transition toward more adequate child care, school health programs may find it necessary to encompass more of the individual health supervision of the child. It is well to recognize that this is only a transitional, and not an ideal, type of program. In the light of this introduction, special problems of this age period will be considered.

Physical.—Physical growth is steady during these years and reflects general health and nutritional status. The latter should be reviewed regularly. During the latter years of this age period, preadolescent growth spurts requiring special nutritional considerations may occur. General health supervision during this age should embody education for parents and child alike to anticipate both growth and early genital changes. Because of special considerations in the school years, certain phases of the physical evaluation will be singled out for special attention.

Vision and Hearing.—Because they are so fundamental to effective learning, objective assessment of vision and hearing should be undertaken and remedial measures implemented as indicated for every child. This involves the development of more adequate screening techniques which can be applied broadly to find those children who require more detailed examination. Studies which are in progress should provide screening techniques which are both adequate and practical. This portion of the physical examination may perhaps better be left to the school health program in which specially trained personnel and facilities may be concentrated. Special educational provisions for children who may profit from these should be available. An effort should be made to detect any background for reading disabilities and lack of educational progress which may have a sensory origin.

Orthopedic.—Orthopedic evaluation to determine whether the child can meet the skeletal and neuromuscular demands of a school situation should be undertaken. Detection of minor disorders is desirable and correction of these or allowance for them in the educational program should be made. Special attention should be given to the capacity of the child to take part in a general physical educational program or in competitive athletics. Because of the importance of physical adequacy, especially for boys, in psychologic development, some insight into physical potentialities and their individual differences should be provided.

Cardiovascular.—Relatively inadequate information concerning cardiovascular adequacy or inadequacy during childhood is available. The considerable increase in cardiac size which occurs during this age period merits more detailed study concerning its practical implications. Since rheumatic fever increases in incidence during this age period, evaluation of cardiac function assumes considerable significance for this reason alone. The incidence of rheumatic fever also emphasizes the importance of prompt attention to respiratory infections re-

gardless of severity and the application of prophylactic measures as indicated. Under all circumstances, cardiac evaluation should be undertaken only by those who recognize the hazards of emotional problems which may be engendered by repeated examination. Adequate consultation services may help to minimize the possibility of anxieties relating to cardiac function.

Dental.—The fact that permanent dentition makes its appearance during this age period, makes provision of adequate dental examination and reparative work essential. The development of better methods of dental caries prophylaxis is awaited; existing methods such as a proper oral hygiene educational program, proper nutrition, and good general health must be emphasized. Recently, health officers have become favorably impressed with water fluorination in caries control. Dental services, just as medical services, should have continuity and, therefore, center about the individual dentist whether in private practice, a clinic, or the school health program. The training of dental hygienists should assume greater importance as more adequate dental care facilities are provided. The orientation of the dentist toward prophylactic dental practices will undoubtedly require increases in dentists trained as well as modifying the educational content of their teaching. Orthodontic care must also become more generally available. Steps toward increasing the training of such specialists should be undertaken at the earliest possible time because of the prolonged training period required for the development of adequate skills. The high incidence of rejections because of dental disorders during the military mobilization of World War II was a serious reflection on the lack of care of the permanent dentition during childhood.

Emotional Development.—Emotional problems may interfere seriously with the learning process. The school situation should be one of the positive forces in any mental hygiene program. Through an understanding of human behavior, skilled teachers can provide in terms understandable to the specific age group some comprehension of emotional development and interpersonal relationships. This is obviously an intimate part of an educational system rather than health supervision, but is illustrative of the interdependence of all professional personnel who work with children. Physicians or psychiatrists who work with the child and family have much greater opportunities for successful functioning if they also work with educators. Certainly the training of teachers should encompass preparation in the emotional development of children. Guidance facilities available to child, parents, faculty, and physician alike should be developed in schools and work closely with health and social agencies.

Accidents.—Accidental death is the greatest single cause of mortality in childhood. As a result, educational programs for parents and children should be developed for accident prophylaxis. Physicians particularly should play a more active role in developing safer motor vehicle design and practices since vehicular accidents constitute the largest grouping of accidents. Suggestions for the avoidance of accidents should become an activity of all health personnel as home visits are made.

ADOLESCENCE

Introduction.—Health supervision during adolescence has been the most neglected of all age periods preceding adulthood. This has been due in part to lack of education and also to a general confusion concerning whether the health of the adolescent should be supervised by the physician interested in adult patients or in young patients. Since the physician caring for infants and children is concerned with active growth, it has come to be generally accepted that the adolescent, because he too is characterized by rapid growth, should be cared for by the same personnel.

The changes in physical, physiologic, and emotional status during adolescence are profound and therefore merit special consideration. Since the effectiveness of the adult depends to a considerable extent upon the success with which he traverses adolescence, skillful guidance with attention to the problems of each individual is fundamental. The general misunderstanding of adolescents in our culture tends to create feelings of inferiority and to cause them to be subject to ridicule. Widespread education toward a better understanding of this age period is essential to correct this situation.

Physical Care.—Adolescence is characterized by rapid growth in body length and mass. Although the entire period of adolescence extends for several years (from "childhood to adulthood"), the "growth spurt" may predominate in a period of several months to several years. Careful supervision of the nutrition of each individual, particularly to be certain that protein, calcium, and vitamin D are adequate in the diet, is important. Unless nutrition factors are adequate, muscle mass may not be developed adequately. This may account for the relatively poor musculature of many of our young adults. It has been suggested that skeletal disorders such as slipped epiphysis and epiphysitis may have their origins in inadequate calcium and vitamin D intakes. The relatively high incidence of "adult" tuberculosis during this age period may in part be due to inadequate dietary intake. Certainly, these are not the sole considerations; adequate dietary intake of all essential food factors assures the attainment of greatest physical potentialities.

Economic factors relating to poor dietary intake must be appropriately considered in the health program as solutions are worked out for each family. Also to be considered are emotional and cultural patterns of the adolescent which predispose to inadequate dietary habits when adequate food is available.

Concomitant with general body growth, sexual maturation occurs. Proper sex education in terms understandable to each child should be progressive and prepare the way for understanding these changes as they occur. Particular emphasis should be given to the individual variations of the chronologic age at which these changes make their appearance. Careful physical examinations for any genital and endocrine abnormalities for which a predisposition exists at this period should be undertaken. Hyperthyroidism may be misinterpreted as a purely emotional problem unless skillful evaluation is periodically performed.

Emotional Development.—The emotional development of this period prepares the adolescent to assume his role

as a mature citizen in our society. The specific problems of accepting one's own physical status and adjusting to it are often attended by anxieties which appropriate psychologic guidance can help to resolve. The establishment of heterosexual relationships by each adolescent is also attended by individual problems. Greater independence associated with separation from parents and increasing concern over real problems of the outside world are often most difficult in a culture which frequently overprotects the adolescent only to precipitate these problems upon him abruptly at a later date. The idealism often characteristic of the adolescent and so often subject to ridicule represents a wholesome tendency by which the individual's role in society becomes established. In general, adolescents should be encouraged to assume both intellectual and practical responsibilities gradually with due allowance for mistakes which are part of "practicing at being grown up." Health supervision in the clinic or the physician's office can encourage this gradual progression toward maturity. Psychiatric and psychologic consultation services should be readily available for individual problems. If there has been longitudinal observation of the development of the child, well-trained professional personnel can anticipate to a considerable extent the character of problems which will develop in adolescence.

A neglected phase of adolescent care has been a program for providing the adolescent with an understanding of interpersonal relationships. Experimental programs in education designed to provide both teachers and pupils with an understanding of why they behave as they do should ultimately give us some indication of how the daily experiences of the adolescent can be employed to teach an understanding of human behavior. If effectively done, this should ultimately contribute adults to our population who can successfully adjust to the responsibilities of citizenship and assist others in doing the same.

AVAILABILITY OF HEALTH SUPERVISION FOR INFANTS AND CHILDREN

Although the availability of health supervision for infants and children is changing rapidly, it is appropriate to review these services at the time of the American Academy of Pediatrics Study of Child Health Services. At that time, it was found that 2,013 of the 3,067 counties in the United States were without any well-child conferences. Of children under 5 years of age, 31 per cent (4,364,164 children) resided in the counties without such conferences. It was generally observed that these programs were concentrated in metropolitan areas; in some states, practically no well-child conferences are conducted outside of metropolitan centers. Since geographic accessibility is essential to the effective use of these services, this situation is indeed significant.

The absence of well-child clinics does not mean that no well-child supervision is offered. Certainly practicing physicians are currently caring for children as parents request periodic health supervision. However, the lack of supporting personnel which are available to assist the physician through a clinic organization (as indicated earlier) and the sporadic nature of services of this character cannot be considered to approach adequacy.

In the clinics already established, great variability in the quality of service exists. Thus, in many states, these clinics lack the services of nutritionists, psychologic and psychiatric services, and adequate numbers of public health nurses. A few metropolitan areas are doing relatively outstanding work, however.

The lack of services extends to other services as well. Although community agencies provided approximately 4,000,000 dental examinations in children's dental clinics, only 700,000 children received dental service. Only about one child of every fifty in the United States received dental care. Thus the program, inadequate though it is, remains predominantly an examination program. Insofar as public health nursing is concerned, the study revealed that we have approximately one public health nurse for every 2,500 children. It is generally accepted that one nurse for every 500 children is a desirable ratio for an effective program. Thus, we need approximately five times more public health nurses.

Adequate supervision for infants and children will require extension of existing facilities, qualitative improvement of clinics already functioning, and the development of new facilities broadly based in a total community health program. In addition, the development of these programs awaits the extension of training of all professional groups concerned with child care. An alert citizenry increasingly recognizes the significance of child health to our national welfare.

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Clinical Conference

CLINICAL CONFERENCE AT THE BOBS ROBERTS MEMORIAL HOSPITAL

F. Howell Wright, Chairman

Case 1. Malformational Syndrome Suggesting Ovarian Agenesis in Preadolescence

Dr. C. A. Haney (Assistant Resident in Pediatrics).—J. J. McH., an 11-year 11-month-old white girl, was admitted Aug. 23, 1951, because of smallness of stature since birth and bronchial asthma since the age of 2½ years. Her mother, aged 34, is 5 feet 2 inches tall, and her father, aged 40, measures 5 feet 7½ inches. Both parents have several near relatives less than 5 feet 5 inches tall. The patient has a sister aged 9 years, 45 inches high, weighing 56 pounds, and a brother aged 7 years, 37 inches high, weighing 44 pounds; both are in good health. The mother was well during her pregnancy with the patient. Following the patient's birth the mother had an early abortion and two more after the siblings' birth. One of the father's brothers has a daughter who, at 18 years, is now 4 feet 2 inches tall, weighs 72 pounds, has a thick tongue, and speaks indistinctly. She left school at 12 years because of low intelligence. Her menarche appeared at about 12 years, attended by completely normal sexual development. This girl's parents were both 5 feet 5 inches tall and over 50 years of age when this, their first and only child was conceived. No consanguineous marriages have occurred in the family.

From the Department of Pediatrics, University of Chicago School of Medicine.

The patient was born at term by normal delivery and weighed 5½ pounds. At birth the skin about her neck was loose. One foot was doubled up and turned outward. The backs of the hands and feet were swollen. During the first 20 weeks of life she had severe diarrhea. A tendency to rather frequent, mushy dark stools persists to the present day. Although she was a vigorous baby and a good feeder, she had gained only one pound in weight when 3 months old. At this age, she was hospitalized briefly at another hospital, where the only findings were pitting edema of all four extremities and a rather pronounced anemia. The urine was normal. A diagnosis of "persistent neonatal edema," due most likely to "nutritional anemia," was made. Following this hospitalization, she failed to grow properly in spite of eating well (Fig. 1). Otherwise, her earlier developmental history and school record were perfectly normal. A tonsillectomy was done at age 3 years. In addition to a number of specific contagious diseases, she had croup, bronchial asthma, a short-lived eczema, frequent canker sores, and pneumonia (at 9 years). Because of the asthma the family had moved from Illinois to Nevada. No signs of sexual development had been observed at the time of her admission here.

A summary of the girl's early history and present development is given in Table I (last column). At the age

of 12 years, her height of 117 cm. was about average for a child of 6½ years. She had grown only 19 cm. in the preceding five years. Her weight of 19 kilograms was average for a child of 5½ to 6½ years (Fig. 1). However, her skeletal and dental maturation was normal for her chronologic age. There was some osteoporosis on x-ray study.

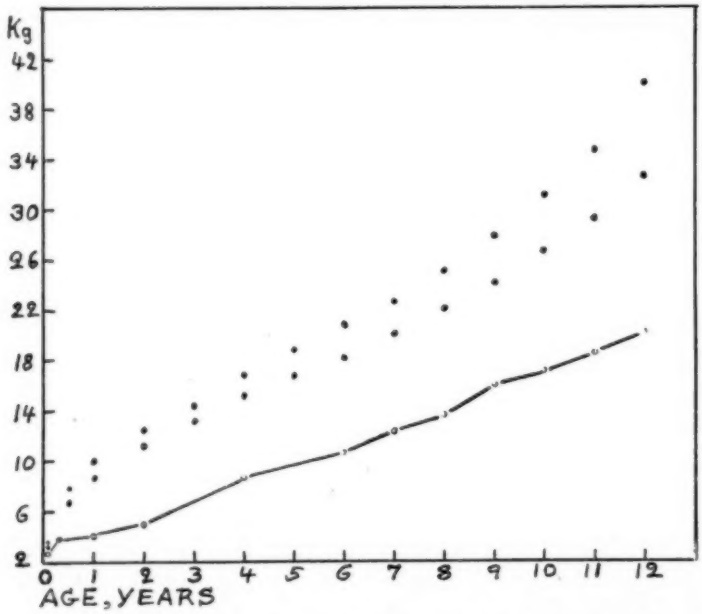

Fig. 1.—Graph showing weight growth curve of patient J. J. McH. (Case 1, Table I, VI) between birth and 12 years of age (solid line). The dotted lines represent the mean and -1 standard deviation for normal weight growth in girls (Iowa Child Welfare Research Station).

The sella was normal. There was no trace of budding breast tissue or of pubic hair (Fig. 2*D*). On recto-abdominal examination (Dr. G. Andros, Department of Gynecology), a midline structure, 0.6 × 1.5 cm. in size, was interpreted to be a subinfantile uterus; nothing but "cords" converging on that structure could be felt in place of adnexa. Colposcopy revealed a vagina 3 cm. long with a smooth mucosa and a vaginal portion of the cervix 0.5 cm. in diameter. Cytologic study of a vaginal smear failed to show any estrogenic activity.

In Table I (last column) there are also listed a number of associated congenital defects or malformations that were found in this girl (Fig. 2*D*). There was a bilateral pterygium colli, or webbing of the neck, more pronounced on the right side. Hair grew down its cranial end; the skin fold stood out 2.5 cm. and transilluminated. There was lack of left sixth nerve function, producing an internal strabismus. According to the history, a left-sided ptosis had been corrected surgically at age 2½ years. There was a slight bilateral epicanthus and a definite facial asymmetry, the right side being larger than the left. A combination of large, deep-set ears with slight hy-

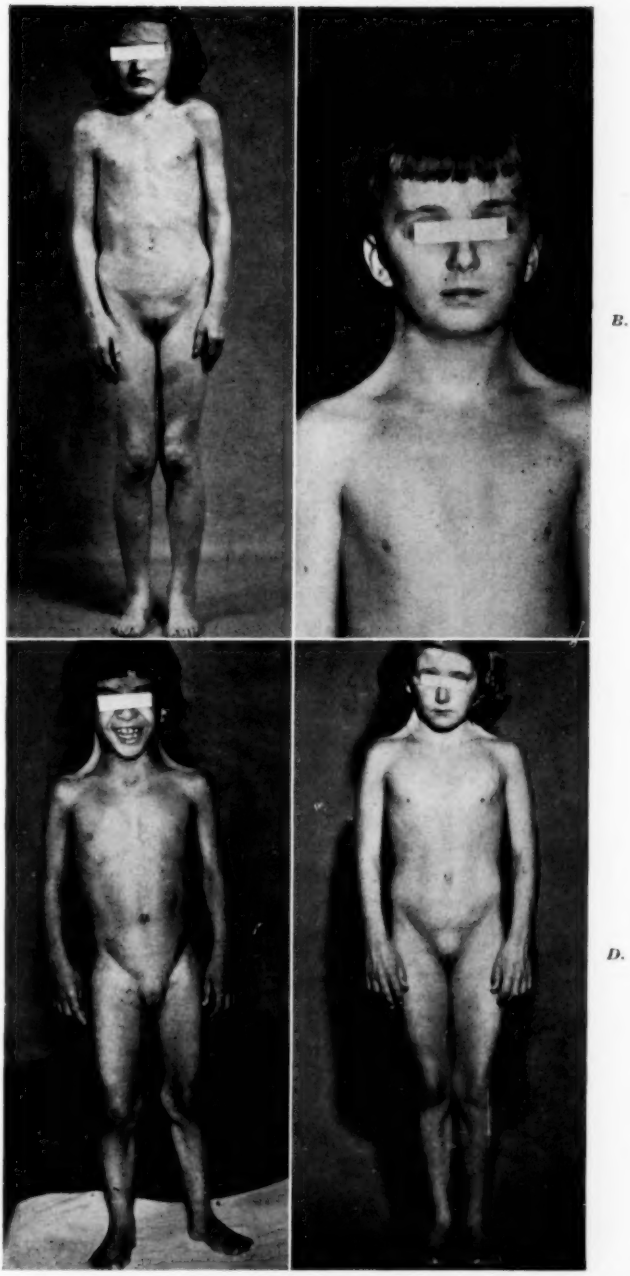

Fig. 2.—*A*, Patient J. L. F., aged 13½ years (Table I, III). Note short neck, "triangular" mouth, complete lack of sexual development, and Café-au-lait spot on left thigh. *B*, Patient S. A. W., at age of 8¾ years (Table I, IV). Note webbed neck, left epicanthus, large deep-set ears, hypoplastic inverted nipples and multiple skin moles. *C*, Patient E. M., at age of 7½ years (Table I, V). Note webbed neck, shieldlike chest, broad shoulders, narrow hips, wide-spaced hypoplastic nipples, mild funnel chest. *D*, Patient J. J. McH., aged 12 years (Case 1, Table I, VI). Note left internal strabismus, small mouth, webbed neck, broad shoulders, shieldlike chest, narrow hips, hypoplastic depressed nipples, moles on skin.

TABLE I. SIX CLINICAL OBSERVATIONS OF PREADOLESCENT OVARIAN AGENESIS (INCLUDING TWO CASES FROM EARLY LITERATURE)

OBSERVATIONS	I FUNKE, 1902	II ULLRICH, 1930	III J. L. F., 1946	IV S. A. W., 1951	V E. M., 1950-1951	VI (CASE 1) J. J. MC H., 1951
Patient's age (yr.)	15½	8	13½	10¼	8¾	12
Mother's age (yr.)	42		34	32	30	34
Other pregnancies	1 normal sister	1 normal older brother	2 normal younger sisters	None	2 normal younger sisters	2 young siblings; 3 early abortions
Birth weight (lb.)	8¼	6¼	6	6¼	4½	5½
Present weight (kg.) (norm.)	39.0 (51.5)*		22.7 (46.5)	25.7 (31.6)	16.2 (27.0)	19.0 (40.0)
Present height (cm.) (norm.)	135 (159)*	114 (123)*	127 (158)	126 (138)	103.5 (130)	117 (150)
Onset of stunting			Birth?	Birth	Birth	Birth
Familial shortness			Parents	Mother's sister	Parents	Mother, siblings, others
Height age (yr.)	10½*	6¾*	8¼	8	4	6½
Skeletal age (yr.)			13	10	8½	11¼
Dental age (yr.)		7	12	10	9	12
Sexual infantilism	+ (no pubic hair)	?	+? (a few pubic hairs)	?	?	+? (no pubic hair)
Size of uterus (cm.)				1.5 × 0.75	±2.5	1.5 × 0.6
Congenital lymphedema	Feet	Neck, right hand, feet		Hands, feet	Rt. foot	Neck, hands, feet
Webbing of neck	+	+	Short neck	+	++	+(Rt.> lt.)
Neuromuscular weaknesses		Bilateral ptosis. Thin facial musculature	Thin facial musculature	0	Thin facial musculature	Lt. ptosis. Lt. internal strabismus

Bilateral epicanthus	0	?	0	+(Left)	–	–
Large, deep-set ears	+	+		–	–	+
Micrognathia	++	++	0	–	+	+
Steep palate	+	+		+	+	+
Nasal voice	+		+	0	+	0
Small "triangular" mouth	+	+	+	+	0	+
"Shieldlike" chest	+	+	0	+	++	+
Hypoplastic mammillae (diam., cm.)	+	+		+(11 mm.)	+(11 mm.)	+ (5 mm.)
Cubitus valgus		+		+	+	+
Curved fifth fingers			+(Rt.)	Short	Lt. short	+
Dystrophic "shovel" nails		+		+	+	+
Spina bifida occulta			+	0	+	0
Intelligence	Good	Good	I.Q. 70	Good	I.Q. 92 Ungraded class	I.Q. 92 (or better)
Associated major malformations	O (Heart normal)	O (Heart normal)	O (Functional heart murmur. I.V. pyelogram normal)	O (Heart and blood vessels normal)	O (Heart and blood vessels normal)	+ (Heart, kidney, see text)
Miscellaneous	None reported.	Ear lobes attached. Umbilical hernia. Diarrhea as a newborn.	Ears standing off head. Rt. central deafness. Elongated digits. Normal lenses. Café-au-lait spot, lt. thigh.	Funnel chest. Skin moles, café-au-lait spots. Overbite. Attached ear lobes. Hypermetropia. Short 4th and 5th toes.	Bilateral shortness of 4th and 5th toes. Funnel chest.	Facial asymmetry. Missing 3rd mandibular molars. Facial freckles, skin moles.

++, marked; +, present; 0, absent; blank space, not known; ?, still undecided.
*German standards used for these "normals."

pognathia was present. Both mandibular third molars were congenitally missing. Her small lips tended toward triangular shaping. The hard palate was steep and narrow, the voice normal. Her chest appeared unduly broad, "shieldlike," especially in comparison with its depth and the pelvic width (Table II). Her nipples were flat, inverted, wide-spaced, and not only "infantile" in the sense of lacking estrogenic stimulation, but anatomically subinfantile in size (according to Dr. Seckel, the areolae measured only 5 mm. in diameter, compared to a normal of at least 9 to 11 mm. in ½-year-old infants, and over 11 mm. in children above 1 year). Another set of anomalies consisted of an increased carrying angle of both arms, inward curving of both fifth fingers with pronounced midphalangeal hypoplasia on x-ray examination, and dystrophic, shovel-shaped nails on both hands and feet. Finally, she had two major associated malformations. A variety of cardiac and vascular findings suggested a congenital anomaly of the innominate artery and, probably, other defects in the aortic arch (Dr. D. E. Cassels). By intravenous pyelography, no right kidney pelvis or ureter could be outlined, while on the left, large deep-set patches suggested a single nonrotated kidney (no retrograde study could be done). The girl's intelligence and personality appeared more mature than the formal I.Q. of 92 would have it. She had facial freckles and numerous moles on the skin.

Urinary and blood laboratory tests, including biochemical data, proved to be normal. Her basal metabolic rate was +12 per cent by the Shock standards. Total serum cholesterol was

TABLE II. TRUNK MEASUREMENTS IN PATIENTS LISTED IN TABLE I*

	I FUNKE 1902 15½ YR.	III J. L. F. 1946 13½ YR.	IV S. A. W. 1951 10¼ YR.		V E. M. 1951 8¾ YR.		VI J. J. MC H. 1951 12 YR.	
MEASUREMENTS (CM.) INDICES (%)	ACTUAL	ACTUAL	ACTUAL	NORM. FOR HT.-AGE (8 YR.)	ACTUAL	NORM. FOR HT.-AGE (4 YR.)	ACTUAL	NORM. FOR HT.-AGE (6½ YR.)
Distance of nipples (cm.)	17		15.7		14		14.3	
Chest circumference (cm.)	70	59	62	60	56	52.7	57	56
Chest depth (AP) (cm.)			14.3	15.8	12.7	12.6	13.4	13.1
Chest breadth (transverse) (cm.)			20.2	20.8	19.1	17.0	19.9	17.9
Chest index (AP: Transverse)			*70.1*	76.0	*66.5*	74.1	*67.0*	73.2
Biacromial breadth (cm.)	26	27	28.7	27.7	23.6	22.9	26.7	25.4
Bicristal breadth (cm.)			22.0	20.9	16.1	17.0	18.6	19.0
Trunk breadth index (bicristal: biacromial)			76.6	75.4	*68.2*	74.2	*70.0*	74.8

*Most normals were taken from Simmons' Cleveland material. The italic index figures are outside normal standard variations. Anterior trunk height indices were normal in Cases III to VI. Complete anthropologic measurements in addition to those tabulated were taken in Cases IV, V, and VI (H. P. G. Seckel).

162.5 mg. per cent, 75 per cent of which were esters. An insulin tolerance test was clearly responsive. Twenty-four-hour urinary creatinine determinations averaged 525 mg. Urinary 17-ketosteroid excretion was 1.8 mg. per day. A follicle-stimulating hormone (F.S.H.) test was negative.

A daily oral dose of 0.25 mg. diethylstilbestrol has been suggested as substitution therapy, without cyclic interruptions for at least a year, to be modified later.* Retrograde pyelography and surgical correction of the squint and webbing are planned for the future. Her final adult growth expectancy (Bayley) is calculated to be 133 cm.

DR. H. P. G. SECKEL (Assistant Professor of Pediatrics).—The clinical syndrome under discussion was originally described by Funke[1] in 1902 and Ullrich[2] in 1930 (Table I). Turner[3] added ten observations in 1938 and suggested an endocrine pathogenesis. Up to 1942, some twenty patients with this syndrome were recorded to have rudimentary or nonexistent ovaries on biopsies or autopsies. In one of these cases, R. Meyer,[4] as early as 1931, found the urinary "prolan reaction-A such as has not infrequently been demonstrated in castrated and old women." In 1941 and 1942, Varney[5] and Albright[6] and their respective coworkers established the association of the clinical syndrome with abnormally high levels of urinary F.S.H. excretion. In two of Albright's patients, the typical ovarian pathology was also verified by peritoneoscopy.

*Cyclic interruptions were started when menarche occurred four months after initiation of therapy.

In Table I the two original cases from the literature, three earlier observations of our own, and the present Case 1 have been tabulated. Photographs of our patients are shown in Fig. 2 *A-D*.

Compared with the internist, the pediatrician is at a disadvantage in making a diagnosis of ovarian agenesis. In his patients sexually infantile appearance, a tiny uterus, barely palpable ovaries, and absent or low urinary gonadotropic and sex hormone levels appear entirely natural. In the 12- to 15-year age group (Table I, Nos. I, III, VI), a suspicion of sexual infantilism due to this syndrome may naturally arise. As a rule, short of laparotomy or peritoneoscopy, the pediatrician can arrive only at a presumptive diagnosis of ovarian agenesis. Yet, the morphological clues of (1) a unique series of congenital bodily defects and (2) smallness of stature since birth seem to be of such diagnostic significance that he should not wait for corroborative laboratory findings or pathologic verification before arriving at a conclusion and planning for treatment.

The malformational syndrome suggestive of ovarian agenesis may be divided up in a number of groups of congenital anomalies: (a) There is bilateral pterygium colli or, in its absence, a short appearance of the neck, as a rule unaccompanied by cervical bone anomalies. As a sort of precursor, the patient's neonatal history often records the presence of nuchal folds and swellings associated with dorsal edema of hands and feet and dystrophy of nails. (b) There are unilateral or bilateral neuromuscular weaknesses, commonly localized in the cranial area, such as ptosis, strabismus, facial weak-

ness, etc. (e) The face as a whole may appear asymmetrical and masklike, as though the facial muscles were too thin. The mouth may seem triangular shaped, "fishlike," the hard palate narrow and steep, and the voice nasal. The ears are often flabby, large, variously misshapen, and deep set as if moving toward the more or less hypoplastic mandible. This represents the slightest degree of so-called otocephaly. Hypodontia occurs. (d) The chest is frequently of a peculiar voluminousness, sometimes described as stocky or "shieldlike." The shoulders are much broader than the hips (Table II). The nipples are widely spaced, flat or inverted, and of quite an extraordinary smallness, even smaller than in a normal infant. The casual observer may tend to pass them over as "infantile," but they are most definitely subinfantile in size. (e) Skeletal anomalies other than the thoracic plumpness are: mild osteoporosis, cubitis valgus, rib anomalies, spina bifida occulta, elongated fingers, shortness and curving of fingers and toes with midphalangeal osseous hypoplasia, etc. (f) Among the major associated congenital malformations there may be found cerebral agenesis of moderate degree, cardiac anomalies (rarely, coaretation of the aorta), gross urinary tract anomalies, and others.

Smallness of stature (with reasonable skeletal proportions) is seen in the majority, but not in all, of the girls with suspected or verified ovarian agenesis. Most authors attribute this microsomia to a genetic, or "primordial," growth deficiency rather than to an hormonal one. Sometimes miscellaneous maladies, such as recurrent infections or ill-defined intestinal disorders, may contribute to the growth retardation. Histories indicating familial shortness are not uncommon. Most of these children have "always been small." Generally speaking, clinical as well as laboratory experience supports the thesis that a congenitally malformed organism has a tendency to be small in size. They also indicate that estrogens do not directly stimulate linear growth but may do so indirectly, i.e., via production of ACTH and adrenal cortical androgen. In therapeutic tests with estrogenic preparations, some authors have observed moderate gains in height but others have failed to do so. Direct growth stimulation by androgenic therapy may, in fact, be worth a clinical trial.

QUESTION.—What was the result of hormone assays in this case?

DR. SECKEL.—Besides showing a total lack of clinical estrogenic stimulation, a negative F.S.H. test, and a low 17-ketosteroid excretion, our own assays contribute very little, as was to be expected. F.S.H. excretion in the urine may be anticipated to rise any time after the age of 12 years, even to abnormally high levels, which then would confirm the suspected diagnosis.

QUESTION.—Could the extreme smallness of the internal genitals, the disproportion between hips and shoulders, and the diminutive size of the nipples be explained on the assumption that circulating estrogens in these children are on an even lower level than is physiologic for normal young girls?

DR. SECKEL.—With present methods of estrogen assays it seems impossible to answer this question. As for tissue responsiveness of the organs listed, it has been shown by estrogenic therapy to be present in these patients. As

matters stand today, I, for one, should prefer to list those findings under the heading of congenital bodily defects.

QUESTION.—Why is it that the shortness of stature in these girls is not interpreted in terms of "hypopituitary dwarfism"?

DR. SECKEL.—This question has intrigued clinical investigators from the very beginning. Albright and others after him have listed some twelve differential diagnostic points which tell how and why the two conditions are different. For the pediatrician a few of them are of outstanding value. For one, we are dealing with mere shortness of stature in ovarian agenesis but with true dwarfism in the hypopituitary patient. Also, most girls in the former group have been born small and continue to grow at a slow rate. Hypopituitary dwarfs, on the other hand, start out with normal heights and weights at birth and continue to grow normally for a few years, but then fall off with growth to an almost imperceptible pace. Furthermore, the present syndrome is one of multiple congenital malformations, while in pituitary dwarfism defects of that sort are distinctly uncommon. As pediatricians, we may add that dental development in the candidate for ovarian agenesis is in complete conformity with chronologic age, whereas delay in dental maturation is unmistakable in the pituitary dwarf: at 15 years or over the latter may still have several baby teeth in the mouth. The same distinction holds good for skeletal maturation. Here the girl with ovarian agenesis illustrates the general rule that, in congenitally malformed children, bone age tends to be moderately delayed in certain areas of the skeleton while in others normality or even prematurity, may be found; in pituitary dwarfism there is considerable uniform delay.

DR. W. R. HEPNER (One-time Instructor in Pediatrics, University of Chicago; now Assistant Professor of Pediatrics, University of Texas Medical Branch, Galveston, Texas).—Two years ago I observed a newborn baby girl, A. E. S., who was the result of a normal pregnancy and delivery and showed proper measurements at birth (weight 3,785 grams, length 52 cm.). With one notable exception she appeared normal on physical, including neurological, examination (Fig. 3*A*). Large loose folds of excess flesh lay at the nape of the neck, suggesting a slight degree of webbing. They felt firm on pressure and allowed slight indentation. The dorsum of both feet and of both lower forearms and hands was markedly swollen and pitted on pressure. There was lateral hypermobility of the knee joints. Both nipples were inverted. The palate appeared high. Plasma proteins and serum electrolytes were normal. The infant died unexpectedly on the eighth day of life. A clinical diagnosis of chronic congenital lymphangiectatic edema was made.

DR. E. L. POTTER (Associate Professor of Pathology).—On post-mortem examination, associated with an essentially normal fetal uterus and Fallopian tubes were two slender cordlike structures approximately 15 × 2 × 2 mm. Histologically, these proved to consist of ovarian stroma in which no ova could be found (Fig. 3*B*). Lymph channels in the subcutaneous tissue of the entire body were only slightly increased in size and number. The heart

Fig. 3*A*.—Patient A. E. S., mature newborn infant. View of body surface showing massive edema, especially marked over legs and feet, and abnormal folds of skin in the neck.

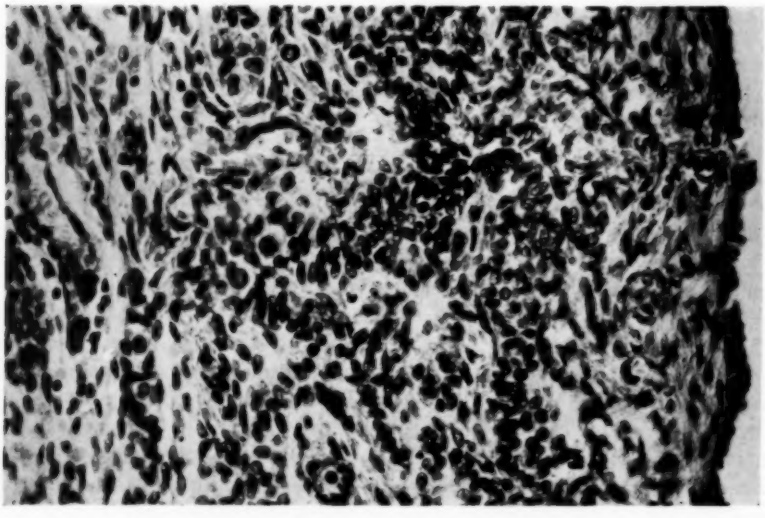

Fig. 3*B*.—Same patient. Microscopic section of one ovary showing complete lack of germ cells (ova).

showed a severe grade of fibro-elastosis and both renal pelves were markedly dilated. The heart lesion was believed to have been the cause of death.

DR. HEPNER.—Ullrich[7] has described newborn girls with swellings in the back of the neck and simultaneous chronic edema of the extremities whom he saw grow up to show true pterygium colli and other signs of the clinical syndrome of ovarian agenesis. He advanced a hypothesis of "congenital autochthonous edema" to explain the bilaterally symmetrical cutaneous changes in these patients. He expressly dissociated this hypothesis from the "myelencephalic bleb" theory of unilateral congenital eye, ear, chest, and arm deformities now known as "status Bonnevie-Ullrich." Dr. Seckel's case might suggest a coexistence and partial overlapping of both syndromes in the same patient.

Case 2. Arteriovenous Fistula in the Neck

DR. CHARLES HANSEN (Intern in Pediatrics).—The patient, K. B., a 9-year-old Negro female, was admitted to the hospital on Oct. 22, 1951, with the history of a cardiac murmur present since 1945. The family history is irrelevant, and prior to the illness which began in 1945, she was considered to be in good health. In 1945 she began to have episodes of abdominal pain with some nausea, vomiting, intermittent fever, and occasional epistaxis. A physician was consulted, a cardiac murmur discovered, and the diagnosis of rheumatic fever and rheumatic heart disease was made. The patient was referred to the University of Chicago Clinics for further study.

She was first seen in the outpatient department in June, 1946. Physical examination at that time was essentially negative except for a moderately loud systolic murmur along the left sternal border, radiating to the apex, and a loud continuous murmur in the right anterior neck, heard from the clavicle to the mastoid and maximum about the midneck. This murmur radiated into the skull on the right and was well heard over the upper thoracic spinous processes and in the upper anterior thorax on the right. The heart rate was 86 per minute and the blood pressure 90/60 mm. of mercury. The electrocardiogram was normal. Bradycardia could not be elicited by occlusion of the right carotid artery, but the neck murmur was reduced and the precordial murmur disappeared with this maneuver. The oxygen content of blood in the right jugular vein was 2.1 volumes per cent higher than in the left. A diagnosis of congenital arteriovenous fistula involving the right carotid artery and jugular vein was believed established and surgery was recommended and refused. She was seen at rare intervals in the clinic subsequently. She had no evidence of circulatory disturbance and no complaints. The murmur in the neck persisted.

At the present admission the essential physical findings were related to the cardiovascular system. The heart rate was 72 per minute and the blood pressure was as follows: left arm, 96/62; right arm, 94/62; left leg, 142/98; right leg, 142/98 mm. of mercury. There was no cardiac enlargement. On auscultation the findings were the same as in 1946. There was a grade 2 systolic murmur along the left sternal border, radiating to the apex. The loud continuous murmur in the right neck was probably louder

and it radiated even more widely. Occlusion of the right carotid artery did not change the murmur, but pressure over a small area lateral to the vessel greatly reduced its intensity without completely obliterating it.

Laboratory findings included a normal urine, a negative serology, red blood cell count of 4,050,000, hemoglobin of 11.5 grams, and a normal white blood cell count and differential.

X-rays of the chest, skull and an angiogram of the right carotid artery are shown.

DR. DOUGLAS N. BUCHANAN (Associate Professor of Pediatrics).—The x-ray photographs demonstrate that on the right side the orbital surface of the great wing of the sphenoid bone is absent (Fig. 6). This is a solitary defect. The orbital portion of the ethmoid bone is intact.

The angiograms (Figs. 7 and 8) did not demonstrate any abnormality of the carotid vessels on the right side.

DR. CASSELS.—The history and physical findings are a modification of a common experience in the clinic. A

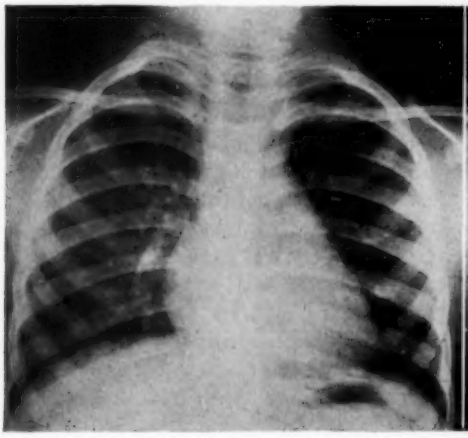

Fig. 4.—Posteroanterior chest x-ray, 1946.

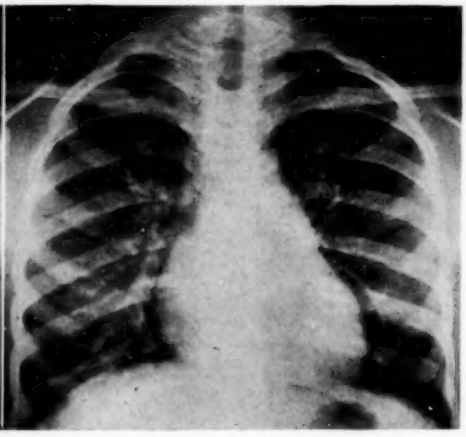

Fig. 5.—Posteroanterior chest x-ray, 1951.

DR. DONALD E. CASSELS (Associate Professor of Pediatrics).—Neither the chest film in 1946 (Fig. 4) nor the one in 1951 (Fig. 5) shows any gross abnormality. In 1946, it was thought that the heart was perhaps a little large, with the apex a little full, and the pulmonary vascular markings a little increased. The film taken on the present admission demonstrates the heart and lungs to be within normal limits. Skull films were taken and an angiogram made.

diagnosis of rheumatic heart disease is made when abdominal or extremity pains are associated with a cardiac murmur, even though the murmur may be functional in origin. The functional murmur heard along the left sternal border in children most frequently has its origin in the neck, usually on the right, and therefore routine auscultation of the neck is the best way to determine whether the murmur heard is intracardiac in origin, when it will be maximum over some area of the

precordium, or whether it is extracardiac in origin, arising in the great vessels of the neck. This functional murmur in the neck may be quite loud, and may radiate into the skull. It is frequently continuous or nearly so, and has been described as a venous hum. However, careful auscultation and palpation identify it as synchronous with the carotid impulse, and I believe that it usually[8] originates in some peculiarity of origin of the right carotid artery from the innominate artery. It changes, or even disappears, on change of position of the head, or on lifting the head, or by pressure on the carotid artery. When this change takes place locally, the precordial murmur disappears.

The neck murmur in this patient is much louder than this functional murmur and changes in position of the head do not alter it. There is a slight thrill in the area of maximum intensity, but this may be present also in functional murmurs in the neck. There is, however, a single point where pressure so greatly reduces the intensity of the loud roar that it must be presumed that an arteriovenous fistula has been at least partially closed. It was my belief in 1946 that this fistula involved the carotid artery and jugular vein, since there was a significant difference in the oxygen content of blood from the right and left jugular veins, but the angiogram (Fig. 7) shows no direct communication. There

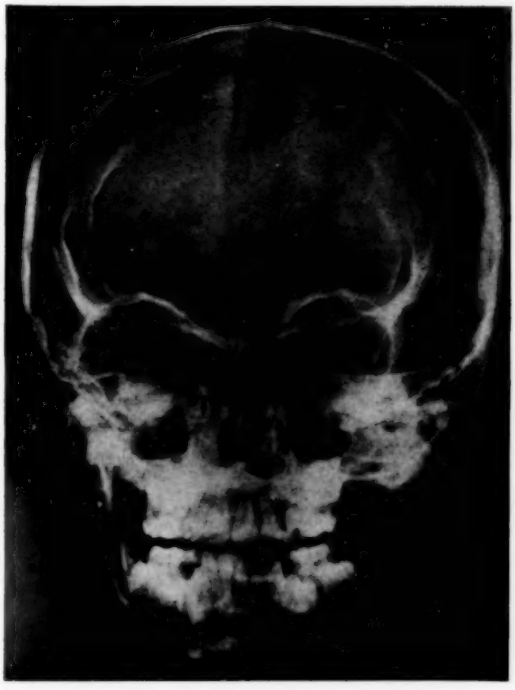

Fig. 6.—Anteroposterior view, skull.

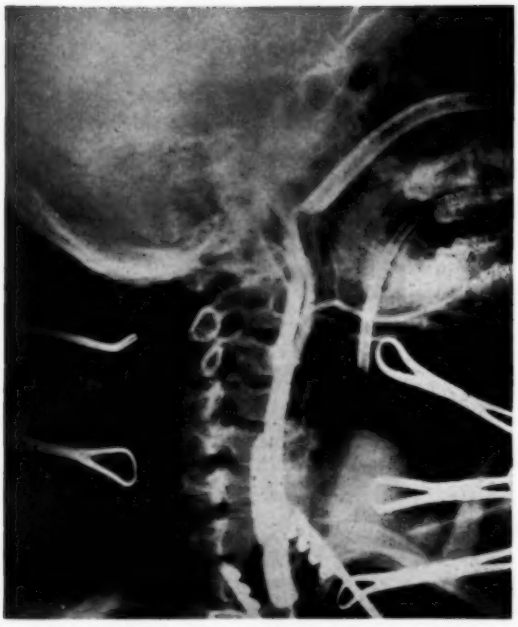

Fig. 7.—Angiogram, right carotid arteries. No direct arteriovenous communication is demonstrated.

Fig. 8.—Anteroposterior view of head during angiography. The right half of the circle of Willis is normal.

is adequate clinical evidence of an arteriovenous fistula in this area, but it is smaller than anticipated and it has not been adequately localized for surgical intervention. It is believed that a radical neck dissection is not warranted unless some signs of circulatory embarrassment occur.

Congenital arteriovenous communications should be common when the embryology of the arteries and veins is considered, since they arise from a common capillary plexus, and the formation of a vessel requires both constructive and destructive changes. They have been found throughout the body, but are most common at the base of limbs and the neck. They sometimes occur intracranially as a communication between the posterior communicating artery and the great vein of Galen. Holman,[9] Reid,[10] and others have discussed arteriovenous communications in detail.

DR. KLARA PREC (Mead Johnson Fellow in Pediatrics).—How large do arteriovenous aneurysms have to be before they produce clinical signs, such as cardiac enlargement or tachycardia?

DR. CASSELS.—The general rule is the larger the vessels involved and the more proximally located they are in reference to the heart, the greater is the clinical significance. The duration of the arteriovenous shunt is also important since relatively small communications present for a long time may cause cardiac enlargement. While the vessels involved have not been identified, the very loud murmur suggests that there very probably will be circulatory disturbances sometime in the future. Table III lists the effects of an arteriovenous fistula on the circulation. Of these effects, numbers 1, 5, and 8 were demonstrated to be present. Number 3, a slowing of the pulse upon closure of the fistula, could not be established in the patient. This phenomenon was first observed by Nikoladini[11] in 1875, although the bradycardia is commonly named after Branham[12] who described it in 1890.

TABLE III. EFFECTS OF AN ARTERIOVENOUS FISTULA ON THE CIRCULATION

1. Development of a continuous thrill and murmur, with systolic intensification.
2. A fall in the mean arterial blood pressure.
3. An acceleration of the pulse rate.
4. A rise in venous pressure distal to the A-V communication, and sometimes proximally.
5. Increased venous oxygenation proximally.
6. Dilatation of the heart and of the artery and vein proximal to the communication.
7. Development of extensive collateral circulation about the fistula.
8. Increase of the blood volume.
9. Increase of the cardiac output.
10. Decrease of coronary blood flow.

Fig. 9 shows the blood volume in relation to the blood volume in another form of extracardiac fistula, the patent ductus arteriosus. The increase in volume in the two cases of congenital arteriovenous fistula in the right neck is about the same magnitude as the increase in patients with patent ductus arteriosus.

DR. DUNLAP OLESON (Instructor in Pediatrics).—Can you relate the bony defect in the skull to the vascular anomaly in the neck?

DR. CASSELS.—The defect in the skull lies lateral to the internal carotid. The vessel appears to be normal in the angiogram and there are no visible vascular abnormalities in this area (Fig. 8). However, the bony defect on the same side as the vascular anomaly suggests that they are related, but this has not been proved. There

is no vascular abnormality in the fundus and there is no proptosis.

DR. F. H. WRIGHT.—Would you expect that, if your prediction is correct and circulatory embarrassment or cardiac failure occurs, there will be a fall in diastolic pressure and a widened pulse pressure?

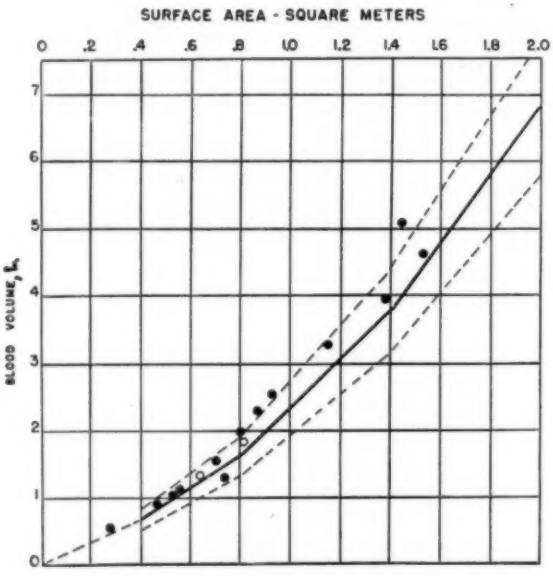

Fig. 9.—The blood volume of the patient (lower open circle) in relation to the blood volume in patients with another type of arteriovenous communication, the patent ductus arteriosus. The mean normal value is indicated by the solid line, and two standard deviations by the dotted lines. (From Cassels and Morse: J. PEDIAT. 31: 490, 1947.)

DR. CASSELS.—This change in blood pressure is related to the degree of shunt. I suppose that if circulatory distress occurs, this indicates a significant shunt and the blood pressure changes therefore would be present. They are not present now.

DR. PREC.—What is the relationship between acceleration of pulse and blood volume?

DR. CASSELS.—It is generally agreed that acceleration of pulse occurs immediately following the experimental production of an arteriovenous fistula. In fistulas of any magnitude, tachycardia is seen in patients. This is more prominent than are increases in blood volume. It seems unlikely that there is any direct relationship between the two. The cause of the tachycardia is not clear. It has been suggested that it is due to an increased cardiac output or to the cardio-accelerator Bainbridge reflex.[13] Lewis and Drury[14] believe that the bradycardia which follows closure of a peripheral arteriovenous fistula is vagal in origin since it is abolished by atropine.

DR. BUCHANAN.—In the days before we had arteriograms this girl would have been explored surgically and the cause of the bony erosion of the orbit

discovered. In all probability she would have been cured. Now that these techniques are available, nothing is done unless there is a pin-point anatomical diagnosis. It is one of the difficulties caused by the advancement of medicine.

DR. CASSELS.—Following the arteriograms, the neurosurgeon and I discussed at some length, before anesthesia was stopped, the proper disposition of the patient. He felt that a rather blind dissection of the neck might not identify the fistula, and would be a considerable undertaking. We thought that should circulatory embarrassment and cardiac enlargement occur in the future, surgical exploration would have to be undertaken. While perhaps this plan is too conservative, I do not believe that the patient has been jeopardized by waiting.

DR. OLESON.—How many cases of congenital arteriovenous aneurysm are seen?

DR. CASSELS.—I see one or two a year.

Case 3. Chronic Cholecystitis and Cholelithiasis in a 2½-Month-Old Infant

DR. LAURENA BOOKER (Intern in Pediatrics).—This 2½-month-old male infant was brought to the Out-Patient Department by his mother who had noted that his skin had been yellow from the time of release from the nursery, and that it had darkened recently.

The parents are of German-Irish extraction, and there are two other living children. During the pregnancy with the first two, the mother had albuminuria; and during the last pregnancy, symptoms of toxemia developed which indicated an interruption of the pregnancy in the thirty-third week of gestation.

The patient was delivered by cesarean section under local anesthesia at the Chicago Lying-In Hospital. The birth weight was 1,590 grams. In the birthroom he was given 20 c.c. of the mother's blood via the umbilical vein and 2 mg. of vitamin B_{12} subcutaneously. He was sent to the premature nursery in good condition and placed in an Isolette with oxygen and humidity control, where he did well except for brief episodes of cyanosis at 12 and 48 hours of age. After this his course in the nursery was uneventful. Feeding consisted of breast milk from the Chicago breast milk station for the first 26 days of life, but his weight gain was unsatisfactory, and a formula of half-skimmed milk with 8 per cent Dextri-Maltose was substituted. He gained well on this formula, and cereal was added during the last week in the premature nursery. He was discharged on his fifty-fourth day, weighing 2,475 grams. No jaundice was noted at any time during his hospital stay.

After discharge from the nursery, he continued to eat well and to gain weight on an evaporated milk formula, diluted two-fifths at first, and later increased to a three-fifths dilution, supplemented by strained cereals, fruits, and vegetables. He seemed well, showing no lethargy, nausea, vomiting, bleeding tendencies, or other symptoms. However, at the time the mother took the baby home from the nursery, she noticed that his skin was yellow and his stools were light. As time went on, she noted that the skin and sclerae were increasingly more yellow, and that the urine was dark and the stool remained light. No history of exposure

to persons having infectious hepatitis, jaundice, or other illnesses could be elicited. The mother received no injections during pregnancy but venipunctures for serology had been done during the last three months before delivery. The infant had received mother's blood intravenously and vitamin B_{12} in the birthroom, and vitamin K in the nursery. Otherwise his skin was not punctured by needles, there or after discharge.

On admission to Bobs Roberts Hospital, physical examination revealed a small, active, healthy looking, intensely jaundiced white male infant, appearing much younger than 2½ months of age. The skin and selerae were icteric. The right lobe of the liver was firm and the margins were palpable 3 cm. below the right costal margin. The eye grounds showed no abnormalities. Otherwise, the physical findings were within normal limits for a premature infant. The stool was very light yellow and pasty in consistency. A tentative diagnosis of obstructive jaundice was made.

The laboratory findings were as follows: hemoglobin, 10.7 grams; red blood cell count, 3.54 million; white blood cell count, 16,450; platelets, 326,000; reticulocytes, 1.0 per cent; differential, 41 per cent polymorphonuclears, 37 per cent lymphocytes, 21 per cent monocytes, 2 per cent eosinophils; hematocrit, 37 per cent. The mean corpuscular volume was 104; mean corpuscular hemoglobin, 30; mean corpuscular hemoglobin concentration, 29. The fragility test showed: patient: hemolysis, began at .42 per cent NaCl, complete at .36 per cent NaCl; control: hemolysis, began at .42 per cent NaCl, complete at .36 per cent NaCl. Urine was negative for reduction, albumin, and cellular elements. Blood Chemistry: Bilirubin was 5.5 mg. per cent direct, 7.2 mg. per cent indirect; alkaline phosphatase, 7.7 units; cephalin flocculation, 2+; thymol turbidity, 3.4 units; nonprotein nitrogen, 44.9 mg. per cent; total protein, 6.5 Gm. per cent; albumin, 4.7 Gm. per cent; globulin, 1.8 Gm. per cent; albumin/globulin ratio, 2.6. Fecal urobilinogen was not detectable in a twenty-four-hour specimen. Urine urobilinogen was 0.2 unit in a two-hour afternoon specimen.

The patient's blood type was 0. The mother's blood type was not recorded here, but subsequent events ruled out the possibility that injection of the mother's blood was the source of the trouble.

X-rays of the long bones showed a bone age earlier than the patient's stated age, but no evidence of syphilis.

The provisional diagnosis of obstructive jaundice on the basis of congenital malformation of the bile ducts was made, and the patient was explored surgically by Dr. Dwight Clark. At operation, a mass was found plastered up against the liver, with the duodenum attached. When this was dissected out, a fibrosed gall bladder was found, with multiple gallstones inside. The thickened wall and adhesions were typical of a chronic inflammation. The common duct was irrigated with several cubic centimeters of saline without obstruction. The gall bladder was removed.

The postoperative course was uneventful except for several episodes of distention—the first, with acute onset and severe distention was probably acute gastric dilatation; later, milder episodes were more likely related to air swallowing with vigorous crying.

The first postoperative stool, two days after operation, was dark green and sticky. It did not contain blood. Subsequent stools have been light yellow, but darker than those preoperatively. Urine is essentially unchanged.

Laboratory studies on the fifth postoperative day revealed fecal urobilinogen, 5.34 mg. per 100 Gm.; urine urobilinogen, 0.12 unit (approximately one-hour specimen).

Jaundice of the skin is beginning to clear slightly now, on the seventh postoperative day.

Final diagnosis: Chronic cholecystitis, and cholelithiasis in a 2½-month-old infant.

DR. MARVIN LEWIS (Assistant Resident in Pediatrics).—The baby's mother called the clinic for an appointment seventeen days after discharge from Lying-In. She complained that the baby cried continuously, keeping the neighbors awake. She had been to a physician who had decreased the baby's food intake as compared with the discharge formula and stopped iron medication. Upon examination at the first clinic visit, the child did not appear grossly jaundiced although there was a suggestion of a muddy hue to the sclerae. The mother stated that she thought the child had been slightly yellow since she brought him home. The diet was regulated and iron reinstituted.

The mother and baby returned five days later, both much happier. The baby had gained weight but had developed a marked degree of jaundice in the interim. Dr. Senz saw the baby with me at that time and the baby was admitted.

DR. STEPHEN MAYKA (Assistant Resident in Pediatrics).—You said the urine was normal. Was there bile in the urine?

DR. BOOKER.—Bile pigments were found in the first two specimens examined.

DR. DWIGHT CLARK (Professor of Surgery).—At operation we found a mass located in the region of the gall bladder. I did not know what it was, so as I always do when I get into trouble, I called Dr. Humphreys. She said that it was a granuloma of some kind from the gross appearance. We took out the granulomatous mass and Dr. Humphreys can tell you about the pathology. We exposed the common duct and the cystic duct. The common duct seemed dilated, but we could not find a stone. We probed the common duct through the cystic duct, and could get the probe into the duodenum with no evidence of grating. We injected saline into the duct and it readily passed into the duodenum. We elected not to explore the common duct. I have worried about this since. But we probed it well, found no evidence of stone, and consequently did not explore it. The omentum and the duodenum were plastered around the granulomatous mass. A small cord was found which went from the granulomatous mass to the duodenum. It was cut. Whether this represented a cholecystoduodenal fistula I am not prepared to say. Cultures of the gall bladder showed coliform organisms so that it is possible this was a fistula. Whether the gall bladder condition was a cause or result of the possible fistula, I do not know. I thought it was the cause, but Dr. Humphreys does not think so.

DR. ELEANOR HUMPHREYS (Professor of Pathology).—If this is cholecystitis it would not surprise us in an adult

of 40 years or older. We see it rather often. In conjunction we see a great many bile and pigment granulomas, and some sterile abscesses. On direct smear, we saw gram-negative rods. These were probably hemolytic *E. coli*. There was gall bladder tissue left intact, little contracted remnants after the rupture. In my opinion, it is possible that there was a fistula, but I cannot imagine it as primary or that that was how the pigment got in unless stone formation in the absence of infection can lead to perforation. Part of it was like a sieve, full of abscesses and granulomas. Dr. Pierce saw this and can vouch for it.

DR. MILA PIERCE (Associate Professor of Pediatries).—Dr. Humphreys, do you think that the signs of complete obstruction were due to the kinking of the common duct?

DR. HUMPHREYS.—I really do. We ought to talk to Dr. Clark about that. I have seen exactly this lead to intermittent jaundice in adults. There was one woman who had attacks which were quite severe, then would be relieved. Her gall bladder was out, and the duodenum had fallen into the gall bladder fossa and got adherent there. After an eating indiscretion she would get an obstruction of the common duct which would then be relieved. I think it entirely possible that kinking could do this.

DR. ALBERT DORFMAN (Assistant Professor of Pediatries).—Watson believes there is a difference in the fecal urobilinogen in cases of obstruction with stones with infection as compared to tumors and infants with congenital atresias. In all children with congenital atresias there is no urobilinogen in the stool or urine. It is quite interesting that this child had some urobilinogen in the urine and none in the stool.

DR. HUMPHREYS.—Metabolism may come in another way. I crushed some of these stones, and there was no hint of cholesterol crystals. A baby's cholesterol metabolism is probably not at the adult level.

DR. DORFMAN.—Do we have a blood cholesterol?

DR. BOOKER.—No.

DR. CLARK.—One other interesting thing at operation was that the liver looked quite normal. It was not like a liver seen in atresias. It was not the liver of an obstructive jaundice.

DR. HUMPHREYS.—I think the infection is fairly old and dates back to the nursery somewhere. It is not surprising that at the extremes of life, one does not see the febrile reactions to infection. In my Oak Forest (Tuberculosis Sanitarium) records, there is more than one case of walking lobar pneumonia. One man dropped dead in the bath; he did not complain and had not had enough fever to attract attention. Perhaps the same thing holds true for the little runts.

DR. PIERCE.—A quick search of the literature gives one the impression that the operative diagnosis of cholecystitis in infants is rare, although it is not rare in children over one year of age. In Potter's complete review of the literature in 1928,[15] he collected 226 cases, forty-nine of which were in infants; all were diagnosed at post mortem. The frequency of cholecystitis in malnourished infants is emphasized by the Chilean report by Cienfugos[16] in which histological evidence of chole-

cystitis was found in thirty-five of 100 routine autopsies in infants. This author stresses the high incidence of debility in the autopsy group.

Most of the earlier reports come from the British pediatricians. Still[17] reported fourteen cases in 1898, all of which were diagnosed at autopsy. Associated infections in infants are neonatal sepsis and gastroenteritis. In older children streptococcal infections of the upper respiratory tract, scarlet fever, appendicitis and the typhoid group, and lamblia infestations are more common.

In Potter's analysis, jaundice was present in sixty-four, absent in thirty-four, and not stated in 128 of the 226 cases. The relationship of cholangitis to obliteration of the bile ducts has long been a debatable point. And it is noteworthy that in this patient the condition of the liver appeared to be grossly normal.

Case 4. Regional Enteritis

DR. DUNLAP OLESON (Instructor in Pediatrics).—This 14-year-old white boy entered Bobs Roberts Hospital in August, 1950, with the history of diarrhea and cramping abdominal pain of eight months' duration and a thirty-pound weight loss during this period.

His early history is remarkable only in that he is said to have had a chronic discharge from the umbilicus during the first year of life. He had measles and chicken pox in early childhood and a tonsillectomy was performed at 7 years of age. His parents and two siblings are in good health and there is no history of familial disease.

The boy's present illness dates from October, 1949, when he first complained of relatively mild, intermittent cramping abdominal pain; he had no diarrhea during this period. On Jan. 24, 1950, he suddenly began to experience severe paroxysmal abdominal pain and vomited bile-stained material repeatedly. He was admitted to another hospital where emergency laparotomy disclosed a volvulus about a Meckel's diverticulum. An unknown amount of gangrenous small bowel, including the diverticulum, was resected, and an end-to-end anastomosis of the ileum was performed. The boy did well for three or four weeks postoperatively, then developed a moderate diarrhea with four to six soft, greenish, mushy stools per day associated with considerable abdominal discomfort and occasional vomiting. He began to lose weight and was readmitted to the hospital. A second laparotomy was performed in March which is said to have disclosed numerous adhesions about the terminal ileum and ileocecal valve, and an enterocolostomy was done. The boy experienced little relief from this second operative procedure. He continued to have considerable abdominal discomfort with tenesmus, flatulence, and occasional vomiting. He averaged six to eight soft, mushy, and occasionally liquid stools daily, and ran an intermittent fever. Despite nutritional and vitamin supplements his weight fell from 117 to 86 pounds.

When first seen here the outstanding characteristic on physical examination was marked emaciation and muscular wasting. The skin and mucous membranes appeared normal. The lung fields were clear and no cardiac abnormalities were apparent. The abdomen was scaphoid in appearance and two well-healed right rectus incisional scars were apparent. There was moderate abdominal tenderness, most marked in the right lower quadrant, where a

dilated loop of gas-filled bowel could be palpated. No discrete masses were detected.

Laboratory examination disclosed the following data: hemoglobin, 10.0 grams; red blood cell count, 3.33 million; white blood cell count, 5,300; differential, 24 per cent lymphocytes, 62 per cent polymorphonuclears, 3 per cent monocytes, and 1 per cent eosinophils. Erythrocyte sedimentation rate was 31 mm. per hour (Wintrobe). Tuberculin 1:10,000 was negative. Serum Kahn test was negative. Plasma proteins were 6.0 Gm. per cent, the A/G ratio 2.2. Nonprotein nitrogen on admission was 60 mg. per cent, the serum calcium 13.5, and serum phosphorus 5.6 mg. per cent. Repeated stool cultures demonstrated only *E. coli* and *B. proteus*.

X-ray examination of the colon with contrast media demonstrated an enterocolic fistula at the level of the mid-transverse colon. With continued filling the ascending colon, cecum, and terminal ileum were visualized. The terminal ileum was greatly narrowed over an area of several centimeters and exhibited a bizarre and distorted mucosal pattern. Immediately proximal to the terminal ileum lay a dilated loop of small bowel which showed no recognizable mucosal pattern.

The boy was prepared for surgery with a high caloric diet, Sulfasuxidine, and supplemental oral and parenteral vitamins; he received 1,000 c.c. of whole blood and 2,000 c.c. of plasma in the preoperative period. At operation he was found to have approximately 8 feet of small bowel of relatively normal appearance extending from the ligament of Treitz to the enterocolic fistula. The terminal ileum, cecum, and the blind loop of small bowel were the site of an intense inflammatory reaction with thickening and distortion of the bowel and mesentery, multiple enlarged regional lymph nodes, and many old and fresh adhesions. The appendix, the cecum, and the blind loop were resected up to the level of the enterocolostomy, together with the mesentery and the involved nodes, and the ascending colon was closed. Streptomycin and penicillin were administered postoperatively, and the patient was maintained on parenteral fluids for one week. The postoperative course was surprisingly uneventful, and the boy began to improve clinically and to gain weight.

Gross pathological examination of the resected bowel revealed extensive erosion and granulation of the mucosal surface with areas of ulceration and of pseudopolyp formation. There was marked thickening of the bowel wall and of the mesentery, and microscopic examination of these tissues disclosed the inflammatory lesions characteristic of regional enteritis.

Following convalescence the functional ability of the remaining intestine was studied briefly. The oral glucose tolerance test produced a normal curve. Nitrogen absorption, measured as serum alpha-amino nitrogen following a test meal of gelatin, appeared significantly low; and the vitamin A absorption test failed to produce a rise over the initial fasting levels. The patient was discharged four weeks postoperatively on a low-residue, high-caloric diet with supplemental vitamins. During the first two postoperative months he continued to have occasional mild cramping abdominal discomfort associated with defecation and averaged three to four soft stools daily. During this period his appetite was raven-

ous and he gained 16 pounds in weight. In November, ten weeks postoperatively, he was readmitted with homologous serum hepatitis from which his recovery was rapid and uneventful.

During the past six months the boy has continued to do very well. He has gained weight steadily and weighs 121 pounds at present. He is entirely asymptomatic and has one or two semiformed stools each day. He has returned to school and his activities are restricted only in regard to competitive sports and strenuous physical exercise.

SUMMARY OF DISCUSSION

Regional enteritis, while predominantly a disease of adult life, is being recognized with increasing frequency in children. Its etiology remains obscure. The pathological picture of acute and chronic inflammation suggests an infectious agent but cultures of involved lymph nodes, mesentery, and peritoneal fluid have failed to demonstrate convincingly a specific agent. Diagnosis may present real difficulties. The relatively characteristic history of intermittent fever, weight loss, diarrhea, and abdominal pain may suggest specific enteric infection or ulcerative colitis. In one patient in our series the predominant symptom was massive, exsanguinating intestinal hemorrhage. The barium enema usually reveals a normal colon, but fluoroscopic examination of the barium-filled terminal ileum may show alteration of the mucosal pattern or—in the advanced, cicatricial stage—the "string sign" of Kantor. Barium orally may show areas of constriction or dilatation of the ileum. Therapy in the chronic, obstructive phase of the disease is predominantly surgical.

In the present patient the chief problem following resection centered about the nutritional maintenance of the child. At laparotomy the surgical estimate of the remaining small intestine was eight feet, approximately one-third of the normal amount. There was doubt as to whether this would prove adequate in absorptive capacity for the maintenance of nutrition and for growth. It obviously is. That the boy has absorbed calories in adequate amounts is evidenced by his rapid gain in weight. Despite evidence of reduced fat absorption he has manifested no evidence of deficiency of the fat-soluble vitamins. A not uncommon complication of massive intestinal resection is calcium depletion, due in part to the formation of insoluble calcium soaps secondary to impaired fat absorption; this boy has shown no signs of tetany and has maintained his serum calcium and phosphorus at essentially normal levels.

In general, results with this disease in the pediatric age group have been good. One cannot escape the rather unhappy feeling that a certain amount of undiagnosed abdominal pain in children represents regional enteritis not sufficiently acute or severe to demand the radiological examination which might demonstrate it.

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Psychologic Aspects of Pediatrics

MASTURBATION IN INFANTS

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MASTURBATION is not uncommon in infancy. Twenty-two out of twenty-five children brought with this complaint to the consulting rooms of Still, the eminent English pediatrician, were less than 2 years old when the habit began.

ETIOLOGY

Spontaneous erections are frequent in male infants preceding micturition. They may also follow manipulation of the sex organs. The infant discovers the genitals in the course of his random movements and finds the act pleasurable. It is not known whether the sensation is similar to that obtained from other manipulations of the body, for example, finger-sucking, or whether it has a special quality. Sometimes nursemaids or parents unintentionally induce the habit by stroking the child's thighs as a soothing measure. Local irritation from tight clothes, balanitis, ammoniacal dermatitis, vulvovaginitis, intestinal worms is regarded as the likely etiological factor by most authors. Still attributes the greater frequency in girls to vulval irritation. It is his opinion that the habit starts as a scratching and rubbing to allay the itching and discomfort. This brings pleasure and so is continued. Local irritation may be the mechanism in older infants but it does not explain the habit during the early months of life before infants can be expected to localize discomfort. Moreover such an explanation fails to take into account the different emotional response of the boys and girls to the habit during infancy.

Masturbation has been observed in female infants much more often than in males. Though boys sometimes indulge in the habit with considerable persistence it is questionable whether the habit is ever well developed in them, amounting, generally, only to occasional and random manipulation associated with erection. The intense emotional concomitants seen in girls have not been described in boy babies.

SYMPTOMATOLOGY

The habit in girls may begin during the first few weeks of life. In a patient of Still's, the mother, an intelligent woman, reported that the habit had begun in the first week of life. We saw a child one year old in whom the mother, a schoolteacher, reported that the habit began at one month of age. The act is accomplished by thigh friction, by rubbing the body against a pillow or other object, or by manipulation. One baby 6 months old, observed by us, masturbated only when lying on the back and then almost

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continuously while awake. At times the body is swayed backward and forward with the thighs crossed rigidly. The active phase lasts for some seconds or minutes and is accompanied by grunting, flushing, and an appearance of excitement. The gaze is often fixed and the infants show extreme annoyance if efforts are made to interrupt them. The movements cease abruptly and are followed by general relaxation, pallor, and sweating. In some cases the child appears exhausted and falls into a deep sleep. The habit is practiced many times during the day, only occasionally at night.

The active movements, the glassy stare, the appearance of exhaustion, and the deep sleep which sometimes follows the episode may be falsely interpreted as convulsive or petit mal attacks.

The infants give the appearance of experiencing an orgasm. Indeed the parents often recognize the child's reaction as such. Still speaks of the "sleep that comes with the exhaustion from the orgasm." That females may experience orgasm despite the absence of actively functioning ovaries is well known from observations on ovarectomized women.

There is no reason to believe—as is often stated in the literature—that masturbation in infancy is associated with a neuropathic constitution or with mental deficiency. General health is not interfered with as a result of the habit nor are there, generally, other complaints about behavior. In the patients mentioned in the literature and in those observed by us, there is no indication that unfavorable psychologic factors in the child's environment predispose to the habit. Indeed, the habit has been observed in several cases during the first two months of life before cortical activity can be a factor. However, as the child grows older and becomes increasingly aware of parental concern about the habit, psychic factors become of more importance and may be influential in intensifying and prolonging it. Parental efforts at coercing the child to stop his habit may rouse resistance and cause him to continue it out of spite. As with other habits in children, e.g., finger-sucking, bed-wetting, and so on, the child will resort to his habit more frequently when he is unhappy or bored.

CASE HISTORIES

CASE 1.—G. R., a girl, was born at term by normal spontaneous delivery, weighing 8 pounds 4 ounces (3.75 kilograms). Breast feeding was discontinued after seven days because of fissuring of the nipples. She took the bottle well and gained normally. Solid foods were introduced at 14 weeks and were taken poorly, the child preferring her milk. For the first two years of life she was highly selective regarding her food.

The cup was introduced at 10 months of age and accepted readily. Weaning from the bottle was complete at 14 months. Dentition, motor and speech development were normal.

At about 7 months the child took a great fancy to dolls. Soon afterward she would press her body against a large rag doll to which she was specially attached and make rhythmic movements. At first these episodes occurred only at bedtime but as G. R. approached one year of age she and the doll became inseparable. She carried it about all day and from time to time would throw the doll on the floor, lie down on top of it and rhythmically press her body against it "as in the sexual act." Attempts to disturb her during these episodes resulted in screams and loud crying. She would not release the doll until she felt "sat-

isfied." The parents felt that she "completed an orgasm in her own way."

This behavior continued until 15 months of age. At this time the mother hid the doll, but the child became so unhappy and irritable that the doll was returned. She practiced her habit four to six times during the day and even more frequently at night.

No gross errors in child rearing could be elicited. The parents were sensible and affectionate in their attitudes and accepted the habit calmly. The father was a physician.

After 15 months of age the episodes decreased in frequency and were of shorter duration. She was not as much disturbed when she was interrupted in the act. At 17 months the behavior was exhibited only at bedtime.

When last heard from, G. R. was 4½ years old. She was to all appearances a normal child. The mother described her as "of more or less reasonable temperament. I do not think she differs in any way from the average child. . . . She is an alert, bright, vivacious child." She still practiced her habit occasionally—perhaps three or four times during the preceding two years to the parents' knowledge.

A younger sister started indulging in the same habit—but much less frequently than her older sister—at 22 months.

CASE 2.—H. H., a girl, 5 months old, was brought because of a habit which started at 2 months of age. While lying on her back she would press her legs together, lift them, bear down and get red in the face. This lasted a few moments and was followed by relaxation. The episodes occurred many times each day; in fact whenever the baby lay on her back. The mother stated that sometimes the baby cried as though she was not satisfied.

Except for ammoniacal dermatitis and mild carotinemia, the examination was negative. Several times during the examination, the baby drew up her knees, pressed her thighs together and held her breath as though bearing down. Her face became suffused and the head was drawn to one side.

The mother was advised to decorate the crib with bright-colored ribbons and other objects which might interest the baby.

Eight years later she reported that the habit stopped at 6 to 7 months of age and that the child developed normally thereafter, never to the mother's knowledge, reverting to her habit.

CASE 3.—S. B., a girl, 14 months old, was seen because of a habit. She would cross her legs, grunt, and get red in the face. After some seconds or minutes she would relax, break out in perspiration, and appear exhausted. The mother was a schoolteacher. She reported that the habit started at one month of age. (The baby was born three weeks before term weighing 2.05 kilograms.) The habit had been increasing in frequency and was practiced about three times a day. The child "knows she ought not do it." The mother was determined to break the child of her habit. She slapped her and scolded her but these measures were of no avail. Thumb-sucking had begun at about one year of age.

The child appeared alert and active. Appetite, bowels, and sleep were normal. She weighed 10.3 kilograms.

When the child was 4 years old, the mother reported that her daughter was still practicing her habit, now during the night as well as the day. The child was "of a very nervous temperament." The mother wrote that she was "distraught" at her inability to stop the habit.

PROGNOSIS

So far as is known infants give up their habit completely and do not revert to it later on. Unless the situation has been mismanaged they seem to grow up normally without adverse psychologic residua of any sort.

There are few data on the age at which the habit ceases. One of our three patients stopped at about 3 years, another at about 6 to 7 months. No follow-up was possible in the third case.

MANAGEMENT

Treatment is most effective when the habit is recognized early before it has become well established; hence the importance of early diagnosis. The first step is an explanation to the parents of the innocuousness of the habit, and reassurance as to its favorable outcome and the absence of adverse effects on personality development and on physical health. The parental attitudes should be reviewed and appropriate suggestions made. Scoldings, spankings, threats, shaming, have no place in treatment.

Physical restraints may be useful if the condition is recognized during the first six months of life. If the child masturbates by rubbing her legs together, folding the diaper in such a way as to keep the legs apart may be effective; or the legs may be tied loosely to the crib. After about six months restraints are useless and should be discouraged.

Possible local causes of irritation such as tight clothing, ammoniacal dermatitis, vulval irritation, pin worms should receive attention. Providing the infant with more entertainment in the form of brightly colored ribbons on the crib and baby carriage, rattles, toys, more frequent picking-up, sometimes have a prompt effect in lessening the frequency of the episodes or stopping them altogether.

Benzedrine which lessens sex tension may be tried when the episodes take place principally during the day. For infants under one year of age, the initial dose is 1 mg. once a day in the morning. The dose is increased every other day until a therapeutic or toxic effect is obtained. Phenobarbital or Benadryl may also be useful when the habit is practiced principally at bedtime.

REFERENCE

Still, G. F.: Common Disorders and Diseases of Childhood, ed. 3, London, 1915, Oxford Medical Publications, p. 775.

Comments on Current Literature

HYPERTHYROIDISM

HYPERTHYROIDISM is a condition not commonly encountered in the pediatric age group. However, when this condition does occur in children, difficult problems arise, and decisions concerning management are often of great significance.

In the March, 1952, issue of the *Bulletin of the Johns Hopkins Hospital* Wing and Asper[1] report observations on the use of propylthiouracil in hyperthyroidism with special reference to long-term therapy. Experiences in the thyroid clinic of the Johns Hopkins Hospital over the period of the four years just past are summarized in this publication. During this time, 203 hyperthyroid patients, ranging in age from 14 to 74 years, were treated with propylthiouracil. Seventy-one per cent were between the ages of 20 and 50 years. Seventy-seven per cent had diffuse goiters, 13 per cent had nodular goiters, and 7.9 per cent had recurrent hyperplasia of the thyroid gland following previous subtotal thyroidectomy. Of these 203 patients, forty-four were prepared for subtotal thyroidectomy with propylthiouracil; thirty-four failed to return to the clinic after being under treatment for a few months; eleven were transferred to the care of private physicians; and the remaining 114 were treated with propylthiouracil for varying periods of time. Eighty-seven of these 114 patients were treated with propylthiouracil continuously for a year or longer. Most of the patients studied responded to therapy in a very satisfactory manner. Usually a euthyroid state could be achieved within about 100 days following initiation of therapy.

After considerable experience with this type of medication, the authors found that 300 mg. daily was highly effective as a therapeutic dose, which seemed to be no more toxic than a daily dose of 100 mg. A few patients required higher dosage levels, up to 400 to 500 mg. daily. The initial daily dose of propylthiouracil was divided into three, with oral administration at intervals of approximately eight hours. Maintenance doses were administered at approximately twelve-hour intervals. In each instance the dosage was reduced gradually before discontinuance of therapy was entertained.

While response to medication varies considerably from patient to patient, therapeutic response was definite, as a rule, after ninety to one hundred days of continuous administration. The basal metabolic rate was usually within normal range about ninety days following the initiation of treatment. Sixty-nine of seventy-four patients who had experienced severe loss in weight prior to treatment, gained weight during the ninety-day treatment period. Among eighty-one patients in whom the size of the thyroid gland was recorded frequently, forty-nine (60.5 per cent) showed a definite decrease in the size of the goiter during treatment; twenty-eight (34.5 per cent) experienced no change; and in four (5 per cent), a definite increase in goiter size occurred. During prolonged treatment malignant exophthalmos was not observed in any one of fifty-two patients who had diffuse goiter. In only five of these patients was there a slight increase in exophthalmos.

With respect to remission and relapse, the authors state, "It is well-recognized that if the period of administration of an antithyroid drug is less than six months in duration, relapse of hyperthyroidism is to be expected." Of the 114 cases actively followed by them on therapeutic regimen, sixty-six (41.5 per cent) had had drug discontinued at the time of the report. Among these sixty-six, thirty-eight or 57.5 per cent experienced exacerbation of symptoms following

withdrawal of treatment. In all of the patients experiencing a relapse following withdrawal of propylthiouracil, medication was initiated again. In ten of these thirty-eight patients, a second recurrence of symptoms followed withdrawal after the second therapeutic series. In most instances where recurrences followed withdrawal, development of symptoms took place gradually over a period of six months, and all except a very few of the recurrences were within the year following withdrawal.

In a small number of patients (twenty-seven), long-term continuous medical management has been maintained for periods ranging from twelve to forty-eight months, the average duration being 24.7 months. Nine patients have been treated for more than three years. All these patients on prolonged therapy with propylthiouracil have remained euthyroid showing no deleterious effects. Refractiveness of the disease to the medication has not been observed.

In contrast to thiouracil, which was found to be toxic to such an extent that its clinical use is no longer sanctioned, propylthiouracil has proved to be so much less toxic that its use is considered relatively safe. Toxic reactions to propylthiouracil which do occur include urticaria and dermatitis, fever, loss of hair, leukopenia and granulocytopenia, agranulocytosis, and thrombopenic purpura. In the series reported by Wing and Asper, toxicity to propylthiouracil was manifested by mild leukopenia in twenty-six cases, a granulocytosis in one, eosinophilia in three, urticaria in two, and possibly a lupus erythematosus-like reaction in one. Of all these toxic manifestations, granulocytopenia during therapy was considered the most serious, and of more ominous significance than leukopenia. Only one patient in the series developed agranulocytosis, representing an incidence of 0.5 per cent. There were no fatalities attributable to the toxic manifestations of propylthiouracil.

In general, these authors conclude that propylthiouracil ameliorates thyrotoxicosis effectively, and is a relatively nontoxic agent. The drug is an important adjuvant in preoperative medication for subtotal thyroidectomy, and also can be used for prolonged periods in reasonable anticipation of obtaining eventual remission of the disease. Long lasting remission was obtained in twenty-four of forty-eight patients on withdrawal of the drug after protracted therapy. In the twenty-four patients who had a recurrence of hyperthyroidism, the relapse occurred within six months subsequent to withdrawal of therapy. The authors point out that while ablative forms of treatment in thyrotoxicosis are usually successful in eradicating the disease, constant control is possible by means of prolonged, continuous administration of propylthiouracil. In those patients in whom subtotal thyroidectomy was contraindicated, continuous administration of the drug gave gratifying results.

In the subject of pediatric age in whom symptoms of thyrotoxicosis occur, the decision as to whether thyroidectomy is indicated is always a difficult one. The problem is particularly serious in adolescence during the period of rapid growth. The possibility that the endocrine disturbance is purely a temporary one, and perhaps will right itself as the endocrine status of the child becomes stabilized, poses a question as to whether surgical intervention might be contraindicated. It would seem reasonable that in the pediatric subject, careful control of the hyperthyroid patient by means of this relatively nontoxic drug is to be preferred in general to a more radical surgical approach to therapy.

RUSSELL J. BLATTNER

REFERENCE

1. Wing, Elihu S., and Asper, S. P.: Observations on the Use of Propylthiouracil in Hyperthyroidism With Especial Reference to Long Term Treatment, Bull. Johns Hopkins Hosp. 90: 201, 1952.

News and Notes

Dr. Katherine Dodd, formerly associate professor of pediatrics at the University of Cincinnati, has been appointed professor of pediatrics and head of the department at the University of Arkansas School of Medicine at Little Rock, Ark.

Dr. Andrew L. Chute has been appointed professor of pediatrics and head of the pediatrics department at the University of Toronto Faculty of Medicine. He will also serve as physician-in-chief of the department of pediatrics at the Hospital for Sick Children.

A postgraduate conference for pediatricians will be held on June 5, 6, and 7, 1952, at St. Christopher's Hospital for Children, Philadelphia 33, Pa., under the sponsorship of the Department of Pediatrics of Temple University School of Medicine. The program will include round table and informal discussions of current problems of clinical interest to pediatricians. Enrollment is limited. Further information can be obtained from Miss Ruth Portner.

A list of films entitled "Motion Pictures on Child Life" has been prepared by the Children's Bureau. Over 450 films on the social, medical, mental, and developmental aspects of child life are included. Each film is briefly described without evaluation of the particular film. Copies of the booklet "Motion Pictures on Child Life" can be obtained from the Government Printing Office, Washington 25, D. C., for 40 cents.

The **American Board of Pediatrics** announces the following oral examination:

San Francisco, Calif., June 27, 28, and 29, 1952.

Book Reviews

Die hämolytischen Syndrome im Kindesalter. Priv. Doz. Dr. Conrad Gasser, Stuttgart, 1951, Georg Thieme, 308 pages. Price DM 45.

This monograph is an extensive review of some of the current clinical and diagnostic aspects of hemolytic syndromes in children. The subject material is considered in two main sections. The first part of the monograph deals with the general aspects of the hemolytic syndromes including a thorough discussion of some of the basic factors in abnormal red blood cell destruction and the other section is primarily devoted to a consideration and classification of the specific hemolytic anemias. The material reviewed is recent and well organized, and it is gratifying to note that most of the current contributions of American and British investigators to this subject have been incorporated in the text. Such contributions as the relation of the chemical structure of hemoglobin to the hemolytic state is adequately covered and the recent therapeutic experience with ACTH is included. The text is well documented with an up-to-date bibliography of several hundred references, and the illustrations and photographs are generous and excellently reproduced. The monograph is highly recommended to clinical pathologists, hematologists, pediatricians, and internists as an up-to-date, well-organized, and documented presentation of the present status of our knowledge of the varied hemolytic syndromes that occur in children.

H. G. P.

The Prevention of Rheumatic Fever. Lowell A. Rantz, M.D., Springfield, Ill., 1952, Charles C Thomas, 66 pages. Price $2.25.

In a short monograph, Rantz, one of the recognized authorities in the field, presents the present-day knowledge of the prevention of rheumatic fever. The first three chapters discuss the etiology, and the role of hemolytic streptococcus infection which is looked upon as in some way being responsible for rheumatic fever. The differences in the character and manifestation of streptococcal disease in early childhood, middle childhood, and in older children and adults are stressed. With this as a basis the author turns to prevention and discusses the possibilities and inadequacies

of the prevention of transmission through such measures as isolation, immunization, and chemoprophylaxis. In a final chapter there is a short discussion of the treatment of active and inactive rheumatic fever, and the value of chemoprophylaxis in patients with inactive rheumatism in the presence of streptococcal infection. While the text is short, it gives an unusually clear and well-written picture of the present-day thought and knowledge concerning the prevention of rheumatic fever.

Pathology of the Fetus and the Newborn. Edith L. Potter, M.D., Ph.D., Chicago, 1952, The Year Book Publishers, Inc., 574 pages. Price $19.00.

The aim of the author is well defined in the preface of this book—"to present a brief but complete picture of the infant and to correlate its embryologic development, intrauterine environment and post-natal physiologic adaptation with specific conditions responsible for morbidity and mortality."

Most of the chapters of the book dealing with general subjects, especially those on embryonic development, anoxia, and birth trauma, are excellent. The discussion of infections is the least satisfactory of these chapters. One is surprised to find poliomyelitis and histoplasmosis discussed under prenatal infections. A disregard for the newer classification of bacteria is shown when a paragraph is headed "Paratyphoid; Shigella; Salmonella" and follows a paragraph on typhoid fever.

The brief but clear descriptions of the development of the organ and of the normal condition of the organ at birth, included in chapters on the organ systems, add to the value of this book. In these chapters the author has succeeded in giving clear, complete discussions of pathologic conditions found in the fetus and the newborn infant. The many illustrations which number more than 600 are excellent, both as to selection and reproduction. Considerable space is given to malformations and the illustrations of these are especially good.

The arrangement of the material is sometimes confusing. The development and pathology of the eye are presented in the chapter entitled skeleton. Amyotonia congenita is discussed in the chapter on skeletal muscle and joints. To read the complete discussion of the pathology of erythroblastosis, one must refer to the chapters on blood, liver, central nervous system, kidneys, and skeleton (teeth).

There are omissions which seem to arise from the author's plan to include lesions that are not manifest until beyond the newborn period but only those found in the first three months of life. It is probably because of this age limitation that the author includes generalized vaccinia in infants having eczema but does not mention the generalized skin lesions caused by herpes simplex under similar circumstances. Other omissions may be attributed to the same age limitation. Infantile eczema is not mentioned. Infantile Gaucher's disease is included, but not Letterer-Siwe's disease. Retinoblastoma is only briefly discussed and the hereditary character of this disease is not mentioned. Undue importance should not be attached to these omissions since the author has placed the chief emphasis on diseases of the fetus and the newborn, a field of pathology in which the author's wide experience and knowledge are obvious.

The book should go far in fulfilling the author's expressed desire to stimulate interest in the pathologic changes in the fetus or infant who fails to survive, and to help those who are attempting to discover the reasons for nonsurvival.

M. G. S.

The Doctors Jacobi. Rhoda Truax, Boston, 1952, Little, Brown & Co., 270 pages. Price $3.50.

This is a disappointing book. From the title the reviewer anticipated and looked forward to a good readable biography of the two Jacobis. One, Abraham, was an outstanding influence in the development and course of American medicine, and is rightly called the "Father of American Pediatrics." While the other of the Doctors Jacobi, Mary Putnam, made a distinct contribution in her own field of interest which was the advancement of medical education for women, the importance of her work is relatively little when compared with that of her distinguished husband.

What the biography of the Doctors Jacobi really consists of—and thus the title is a misnomer—is a biography of Mary Putnam Jacobi in which Abraham is included as her husband. The reader reaches page 136 of the 256 pages of text before Abraham is

even mentioned. These pages give a detailed account of Mary Putnam's background, early life, her family and relatives, and her struggles to obtain a medical education and overcome the objections to women doctors which existed 100 years ago. In contrast to these 136 pages, the early life, the education, and the imprisonment in Germany and escape to America of Abraham Jacobi is compressed into a dozen pages. Even the two earlier broken engagements of Mary Putnam, which as far as one can gather from the book did not seem to bother her very much, are discussed in considerable detail, while the two earlier tragic marriages of Abraham are covered in a paragraph of ten lines. The remainder of the book is given to their married life, and to their accomplishments during this period, with the emphasis usually on Mary. The story of Mary Putnam is an interesting one, and this criticism is in no way intended to disparage her work or accomplishments. One can but admire her courage and persistence to overcome the odds that were so much against her in obtaining her medical education. On the other hand, the story of Abraham Jacobi is a far more interesting one and infinitely more important.

The reviewer gets the feeling that what Mrs. Truax became interested in and started out to do was a biography of Mary Putnam, in which Abraham Jacobi naturally came into the story as her husband. There could be no objection to this, and this is really what she has done. But why then, the question arises, was the biography of Mary Putnam Jacobi given the misleading title of *The Doctors Jacobi*. We will leave it to the reader to draw his own conclusions and not express those of the reviewer. It is unfortunate, as the biography leaves the reviewer with the feeling of having been tricked. B. S. V.

Growth and Culture. A Photographic Study of Balinese Childhood. Margaret Mead and Frances C. MacGregor, 58 pages of photography by Gregory Bateson, New York, 1951, G. P. Putnam's Sons, 223 pages. Price $7.50.

This is a most interesting book for the pediatrician although anthropologic rather than pediatric in character. Dr. Mead, the well-known anthropologist and author of *Coming of Age in Samoa*, has collaborated with Mrs. MacGregor in presenting the developmental behavior pattern of Balinese children from photographs by Bateson taken in 1936 to 1939 when he and Dr. Mead were studying Balinese culture. In presenting the material, the general developmental plan of Arnold Gesell based on his studies of New Haven children has been followed. Thus a comparison of the two can be made. While the Balinese and New Haven children go through the same general stages of behavior or development of motor function, consistent differences can be noted. For example, the American child has a greater motor activity due to the limitation of the crawling period of the Balinese child, and the "frogging" posture stage of development of the Balinese child is much prolonged over the American. Both result from differences in the culture of the two as regards the handling of, and cultural attitude toward, the infant.

The photographs are excellent and well reproduced and give a fascinating picture of the life of Balinese children. Not least interesting are two excellent introductory chapters by Dr. Mead on "The Need for Awareness" and "The Significance of Growth in Culture."

Electrokymography. Proceedings of the 1950 Conference at the National Heart Institute, Public Health Service Publication No. 59, Washington, D. C., 1951, U. S. Government Printing Office, 213 pages. Price 75 cents.

The electrokymograph was developed in 1945 through a cooperative effort of Temple University Medical School and the U. S. Public Health Service with the purpose of providing a more adequate instrument for recording the movements of the heart and great vessels. Quite a number of reports on its use have appeared in the physiological and heart journals. A conference of some forty workers who have been investigating the use and value of the instrument was held at the National Heart Institute at Bethesda in 1950, and a group of fifteen papers presented together with their discussion have been collected in this volume. The general conclusion reached was that the instrument was useful in its present form but needed improvement, and that further progress in its evaluation and application is needed before it can be considered for routine clinical use.

Editor's Column

ANOXIA AND RETROLENTAL FIBROPLASIA

RETROLENTAL fibroplasia since its description by Terry ten years ago has been of steadily increasing interest. A marked increase in its incidence has occurred which cannot be accounted for by a simple failure of recognition in the past. Two points stand out: one, it occurs in the more immature of the premature infants; two, the increased incidence has taken place coincidentally with improved pediatric skills and techniques which have lowered the mortality rate for premature infants. Numerous studies have been made in clinics throughout the country in an attempt to find some factor which might give a clue to the reason for its development. Some of the earlier suggestions as to possible etiological factors, as excessive vitamin D intake, and lack of vitamin E, have been discarded.

In the March, 1952, issue of the *American Journal of Ophthalmology*, Szewczyk, of St. Louis, offers an explanation based on his observations as ophthalmologist to the premature service at the Christian Welfare Hospital in East St. Louis, Ill., which has been holding the interest of the ophthalmologists for several months. A preliminary report appeared in the December, 1951, issue of the same journal but it was not until late March that a detailed report of his observations became available.

Szewczyk considers retrolental fibroplasia as an example of the response of immature neural tissue to anoxia. It may be induced by exposing a premature infant to an environment of high oxygen concentration, or by withdrawing oxygen too rapidly from an infant who had been receiving it in the incubator. Either of these may produce vascular changes in the retina which he considers the earliest stage of the disease, and which may go on to the fully developed picture. He further states that in the earlier stages the findings may be reversed by a proper concentration of oxygen.

In 1950 there were 347 premature infants admitted to the service and eight are known to have developed the disease. In the first nine months of 1951 the admission rate increased and it was necessary to shorten the length of stay and wean more rapidly from an oxygen environment. Of 263 infants admitted, twenty developed retrolental fibroplasia. The author discusses the difficulties that were found in maintaining a constant satisfactory level of oxygen in the incubators, due to loss from opening the lid for feeding, faulty valves, and sudden temperature changes affecting the oxygen tanks stored outside the unit. He stresses that if a high concentration of oxygen is maintained in the incubator, the infant must be weaned off very gradually.

There has been much pro and con discussion the last few months among the ophthalmologists as to the validity and importance of Szewczyk's observations. It is a discussion in which the pediatricians can take little part, as the significance of the idea or

theory depends on the ophthalmologic observations, and the vascular retinal changes which the author contends are brought about by differences in the oxygen concentration. These changes have been noted by others, and anoxia has previously been suggested as an etiological factor in retrolental fibroplasia. This, however, is the first report attempting to bring the two together in a cause-and-effect relationship. Whether or not these observations will explain the development of the disease depends on their corroboration by other independent workers. Perhaps if it is not the whole story, his ideas will furnish a clue leading to an elucidation of the problem.

Certain undisputed facts tend to favor the explanation. First, the lesion is essentially vascular in nature; second, it occurs almost exclusively in small premature infants with a high degree of immaturity who have been maintained in an incubator; third, there has been a marked increase in the incidence of the disease since the general use of incubators has kept alive small premature infants who otherwise would not have survived.

In this connection, an observation in another article on retrolental fibroplasia in the same issue is of considerable interest. Ryan reports on twenty-three cases in Melbourne, Australia, of which twenty-one were from one of the two maternity hospitals in the city. There had been no case observed in Melbourne prior to the use of an "efficient oxygen cot" in the hospital. On Oct. 15, 1950, the use of oxygen was restricted to those babies actually cyanosed. Since that time no cases have occurred, and Ryan raises the point as to whether it was incidental or significant.

PALLOR IN SCHOOL CHILDREN

BASED on a study of 1,200 school children in Cambridge, England, Yudkin[1] has recently reported some interesting observations in regard to pallor and the hemoglobin level. Pallor was recorded by the clinical judgment of the investigator, i.e., from the degree of color of the cheeks, lips, and conjunctivae. While this is a purely subjective method of assessment, and the judgment of two investigators would in all probability differ to some extent, it is the method used by the clinician, and no satisfactory method of objective assessment has as yet been devised.

A number of items were included in the examination of the children. Yudkin lists fifteen which by statistical analysis were not related to pallor, and five items which showed an association. The most important associated factor was the nutrition of the child. A direct relation was found between pallor and poor nutrition, and the pale children averaged 2.2 kilograms lower in weight.

Among the fifteen nonassociated factors, which included such items as the incidence of respiratory infection, dental caries, the size of the family, and endurance, the most interesting and important was the relation of pallor and the level of hemoglobin. We quote one of Yudkin's tables showing the exact figures.

Hb (GM. PER 100 ML.)	PERCENTAGE AND NUMBER OF CHILDREN			
	PALE		NOT PALE	
Less than 11	2.8	(5)	3.9	(33)
11-15	92.7	(164)	90.4	(726)
More than 15	4.5	(8)	5.7	(47)
		(177)		(806)
Correlation ratio r = 0.00				

[1]Yudkin, John: The Significance of Pallor in the School Child, Lancet 262: 239 (Feb. 2), 1952.

This finding that pallor was not related to the hemoglobin level led Yudkin to compare some of the other items studied with the hemoglobin level. Among other factors not related to the hemoglobin level were the nutrition of the child, weight, and dental caries. There was a positive association between the level and the size of the child's family. The important conclusion of the study is that "within the range of ordinary children of school age, pallor is no indication that anemia is present. The pale child is no more likely to be anemic than a child of good color with red lips and rosy cheeks."

The significance of Yudkin's studies is not the level of hemoglobin in children of school age. A wide variation is known to exist in "well children," and a 70 to 90 per cent level on a scale using 16 Gm. per ml. as 100 per cent is usually accepted as "normal" for children 4 to 10 years of age. It is rather that pallor in itself cannot be regarded as a sign of anemia.

Yudkin does not go into the question of a genetic or hereditary basis for pallor in the child, nor the question of the complexion in its relation to climate. Physicians who have had the opportunity of closely observing at least three generations of a family, not infrequently observe healthy children with a decided sallowness, or pallor, who have a good hemoglobin level and observe that the same pale color is seen in one of the healthy parents or grandparents.

While the question of climatic differences obviously could not enter into Yudkin's studies, a "ruddy color" in contrast to pallor is often looked upon as being related to climate. Thus a "ruddy complexion" is commonly ascribed to the English. In our own country children in the northern latitudes are usually considered as having a "higher color" than those from the southern. We know of no studies as to the truth of this concept, and it may only be false folklore.